



Protocol Title ***All of Us* Research Program¹**

Sponsor National Institutes of Health (NIH)

Protocol Version Core Protocol V1

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Table of Contents

1. BACKGROUND AND SCIENTIFIC RATIONALE	6
2. OBJECTIVES.....	6
2.1 WHAT IS THE <i>ALL OF US</i> RESEARCH PROGRAM?	6
3. STUDY OVERVIEW.....	8
3.1 CREATING A RESOURCE FOR RESEARCH	8
3.2 MAKING THE RESOURCE ACCESSIBLE FOR RESEARCH.....	9
3.3 STUDY TIMELINE/STUDY DURATION.....	10
4. SELECTION OF PARTICIPANTS.....	10
4.1 ELIGIBILITY.....	10
4.2 INCLUSION/EXCLUSION CRITERIA	11
4.3 VULNERABLE POPULATIONS.....	11
5. RECRUITMENT OUTREACH.....	12
5.1 OUTREACH TO HPO MEMBERS	13
5.2 OUTREACH TO DIRECT VOLUNTEERS.....	13
5.3 OUTREACH TO COMMUNITIES.....	15
6. ENROLLMENT.....	15
6.1 LEVELS OF ENROLLMENT.....	15
6.2 READABILITY OF ENROLLMENT MATERIALS	16
6.3 ACCOUNT CREATION.....	17
6.4 INFORMATION COLLECTED PRIOR TO INFORMED CONSENT	18
6.5 INFORMED CONSENT OVERVIEW	18
6.6 ELECTRONIC CONSENT.....	20
6.7 ADDITIONAL CONSIDERATIONS.....	24
6.8 DATA OVERSIGHT AND CHOICE OF LAW.....	25
7. WHAT IS INVOLVED? PROGRAM PROCEDURES.....	25
7.1 PARTICIPANT-PROVIDED INFORMATION (PPI).....	26
7.2 USE OF PERSONAL HEALTH TECHNOLOGIES	28
7.3 PHYSICAL MEASUREMENTS.....	28
7.4 BIOSPECIMEN COLLECTION	29
7.5 BIOSPECIMEN PROCESSING AND STORAGE.....	31
7.6 ELECTRONIC HEALTH RECORDS (EHRs)	34
7.7 DATA LINKAGE.....	35
7.8 EARLY AND LONG-TERM PARTICIPANT INVOLVEMENT	37
8. RISKS/BENEFITS ASSESSMENT.....	38
8.1 RISKS.....	39
8.2 BENEFITS	41
8.3 RISK/BENEFIT ANALYSIS	42
9. ETHICAL CONSIDERATIONS.....	42
9.1 PAYMENT FOR PARTICIPANTS	42
9.2 GENETIC ANALYSIS ETHICAL CONSIDERATIONS	43
9.3 HANDLING ON-SITE ADVERSE EVENTS	43
9.4 WITHDRAWAL PROCEDURES	43
9.5 DESTRUCTION OF SPECIMENS.....	44
10. ACCESS TO INDIVIDUAL-LEVEL INFORMATION FOR PARTICIPANTS.....	45
10.1 PRINCIPLES OF INDIVIDUAL-LEVEL INFORMATION AVAILABILITY	45
10.2 INDIVIDUAL-LEVEL PROGRAM INFORMATION.....	45

10.3	INFORMATION ACCESS TECHNOLOGIES	48
10.4	INDIVIDUAL-LEVEL INFORMATION ACCESS PROCESSES.....	49
10.5	PHYSICAL MEASUREMENTS—RETURN OF MEDICALLY ACTIONABLE RESULTS	50
10.6	PARTICIPANT-PROVIDED INFORMATION AND EHR.....	53
10.7	ACCESS TO BIOSPECIMEN-DERIVED INFORMATION (NON-GENETIC)	53
10.8	ACCESS TO GENETIC INFORMATION	54
11.	CREATION OF THE <i>ALL OF US</i> RESEARCH PROGRAM RESOURCE	54
12.	POST-ENROLLMENT ENGAGEMENT STRATEGY	55
12.1	CONCEPTUAL FRAMEWORK.....	56
12.2	APPROACH TO ENGAGEMENT.....	57
12.3	RETENTION.....	58
	REFERENCES.....	60

Table of Tables

TABLE 4-1: VULNERABLE POPULATIONS EXCLUDED AT LAUNCH	12
TABLE 6-1: ENROLLMENT DEVICES	17
TABLE 7-1: ESTIMATED DURATION OF PROGRAM ACTIVITIES	25
TABLE 7-2: READABILITY STATISTICS FOR PPI MODULES DESIGNATED FOR USE AT LAUNCH	27
TABLE 7-3: SURVEY COMPLETION TIMES	27
TABLE 7-4: QUESTIONS TO PARTICIPANTS PRIOR TO BLOOD SAMPLE COLLECTION	30
TABLE 7-5: SAMPLE COLLECTION	31
TABLE 10-1: MEDICALLY ACTIONABLE FINDINGS AT THE TIME OF BASELINE PHYSICAL MEASUREMENTS	51

Table of Figures

FIGURE 3-1: PARTICIPANT INTERACTION FLOW	9
FIGURE 6-1: OPTIONS FOR NAVIGATING THE CONSENT MODULES IN ONE SITTING	23
FIGURE 6-2: OPTIONS FOR NAVIGATING THE CONSENT MODULES IN MORE THAN ONE SITTING	24
FIGURE 6-3: SELF-PACED SELF-ADMINISTRATION OF THE CONSENT MODULES	24
FIGURE 7-1: BIOSPECIMEN FLOWCHART	32
FIGURE 7-2: DATA WORKFLOW SAMPLE FOR PARTICIPANTS	37
FIGURE 10-1: ALL OF US RESEARCH PROGRAM INDIVIDUAL-LEVEL INFORMATION: DATA AND RESULTS	46
FIGURE 10-2: DATA FLOW FOR PARTICIPANTS AND HPO STAFF	48
FIGURE 10-3: PHYSICAL MEASUREMENT CARD	52
FIGURE 11-1: CURATED DATASET	54

1. Background and Scientific Rationale

Our current approach to health care is informed by clinical studies that have sample sizes in the thousands, or at most, tens of thousands—meaning that we typically lack the statistical power to make fine-grained predictions about how a given treatment will affect a given individual. As a result, therapies often fail in practice, and most interventions fail to integrate with most patients' own knowledge and lifestyles. Historically, this approach is characterized by a lack of inclusion and diversity in clinical study; that is, the benefits of precise and personalized interventions may not be accruing equitably across society.

Precision medicine is an approach to disease prevention, diagnosis, and treatment that seeks to maximize effectiveness by considering individual variability in genes, environment, and lifestyle. Precision medicine seeks to redefine our understanding of disease onset and progression, treatment response, and health outcomes through the combined analysis of biological, environmental, and behavioral factors that contribute to health and disease. This understanding may lead to more rational disease prevention strategies, more accurate diagnoses, better treatment selection, and the development of novel therapies. This understanding must come from a population that reflects the true diversity and life experiences of those in the United States. A deliberately inclusive strategy that prioritizes groups historically underrepresented in biomedical research should provide enough power for meaningful subgroup analyses and lead to the most precise medicine for these groups.

By combining health-related information from one million or more diverse participants, the *All of Us* Research Program will have the right scale and inclusive scope to enable research for a wide range of diseases, both common and rare. A cohort of this size will have the statistical power to detect associations between genetic and environmental exposures and a wide variety of health outcomes. Outcomes of this research could include novel prevention and screening strategies, earlier and more precise diagnoses, new and more rational use of therapies and improved understanding of why some people remain healthy despite exposures and risk factors for disease.

Coincident with advancing the science of medicine is a changing culture of health care practice and biomedical research that engages individuals as active partners. The *All of Us* Research Program aims to actively engage participants and their advocates in all aspects of the program, including governance, oversight, design, conduct, dissemination, and evaluation. Participants will not only provide their biological, health, behavioral, and environmental data but will be able to access their information, learn about the research being conducted, and be partners in the discovery process. This ongoing partnership between the Program and Participants is described in Section 12 (Post-Enrollment Engagement Strategy).

2. Objectives

2.1 What Is the *All of Us* Research Program?

The mission of *All of Us* is to advance the science of precision medicine and ensure everyone shares in its benefits. To accomplish this, the *All of Us* Research Program

established a set of core values to guide our decisions and actions as the program grows in capacity, reach, and research. We aspire to incorporate these values throughout our journey as our first participants enroll, we collect the first data points, and we plan the first studies:

1. Participation in the *All of Us* Research Program will be open to interested individuals
2. The program will reflect the rich diversity of America
3. Participants will be partners in the program
4. Trust will be earned through robust engagement and full transparency
5. Participants will have access to information and data about themselves
6. Data from the program will be broadly accessible to empower research
7. The program will adhere to the [PMI Privacy and Trust Principles](#) and the [PMI Data Security Policy Principles and Framework](#)
8. The program will be a catalyst for innovative research programs and policies

The overall objective of the *All of Us* Research Program is to build a robust research resource that can facilitate the exploration of biological, clinical, social, and environmental determinants of health and disease. The program will collect and curate health-related data and biospecimens from one million or more individuals who reflect the diversity in the United States; these data and biospecimens will be made broadly available for research uses.

The *All of Us* Research Program is an observational study that will provide the information needed to address a wide range of scientific questions. Resource use is anticipated to be very broad, from the use of aggregate data to the use of individual-level data and biospecimens. This broad usage of data will address a wide range of biomedical and scientific opportunities across diverse populations. Some examples of opportunities that we anticipate can be addressed through judicious use of this resource include:

1. Empowering participants with information and data that may improve their own health
2. Making data broadly available to traditional and nontraditional researchers (including nonprofessional citizen scientists) to develop innovative, new technologies and methodologies
3. Developing quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic factors, and gene–environment interactions
4. Discovering biomarkers that identify individuals with an increased risk of developing common diseases
5. Optimizing screening and prevention strategies based on individual genomic, environmental, and behavioral risk factors
6. Developing tools and approaches for new or improved disease classifications and relationships
7. Using personal health technologies to correlate sensor data, behavior, and the environment with health outcomes

8. Identifying the determinants of safety and efficacy for common therapeutics
9. Using biological data to develop new therapeutic strategies
10. Inviting program participants to participate in clinical trials of targeted interventions and therapies

3. Study Overview

The *All of Us* Research Program aims to enroll one million or more participants from throughout the United States to provide insight into the substantial interindividual differences in physiology, risk of disease, and response to therapy. Participants will be invited to share their electronic health records, if any, and answer health-related questionnaires. Some participants may also be invited to undergo physical measurements and provide biospecimens from which genomic information and other biomarkers may be derived through analytics. The selection of participants to these modules will be based on the desire for demographic diversity. The information and biospecimens collected will become a useful resource for current and future researchers to investigate why some people develop certain health conditions while others do not.

3.1 Creating a Resource for Research

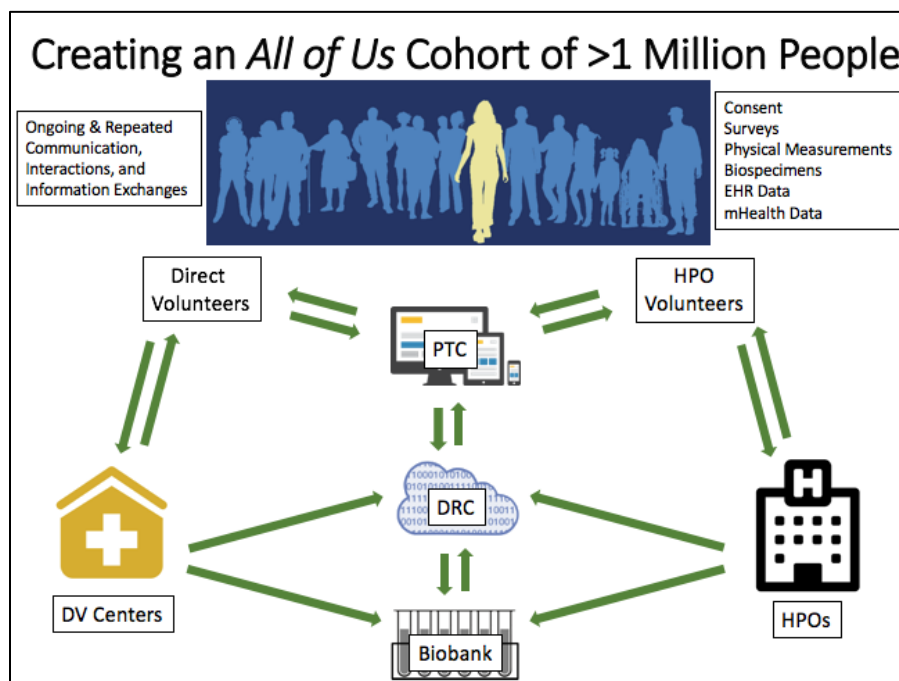
- To build the *All of Us* Research Program, we seek to enroll one million or more participants in one of two ways, illustrated in the Biospecimen Flowchart—Participants may be invited to provide biospecimens (blood, urine, and/or saliva) through their HPO or through their DV partner. Biospecimens will be assayed to generate various biological data, which may be incorporated into participants' study records (see Section 7.4).
 - Passive mobile and digital health data (personal health technology data)—Additional data may eventually be collected from a subset of participants to be determined, through health, wellness and fitness devices, other sensors, and/or mobile applications (see Section 7.2)
1. As direct volunteers (DVs), through digital tools developed by the Participant Technology Systems Center (PTSC) and rendered on a smartphone application and/or a program website, or through a DV partner. A subset of DV partners are enabled to facilitate enrollment.
 2. Through a participating health care provider organization (HPO), for people who are currently receiving care at any of several participating health centers across the United States. Participating HPOs were chosen in the peer review process based on their ability to provide a diverse cross-section of the population as well as for their ability to support and quickly enable the technical and scientific requirements of the study.

Participants will provide some or all of the following:

- Participant-provided information (PPI)—questionnaires and surveys (see Section 7.1, Participant-Provided Information).

- **Electronic health record (EHRs)**—The program seeks to access information from each participant’s EHR. Not all participants will have an EHR, and the process for sharing EHR data to the DRC will differ between HPOs and DVs. HPOs will share EHR data with the DRC for their participants following informed consent. In the future, more participants will be able to share their EHR data with the DRC via the Sync4Science (S4S) technology that is currently in development (see Section 7.6, Electronic Health Records).
- **Physical measurements**—Participants may be invited to provide baseline physical measurements through their HPO or a DV partner (see Section 7.3, Physical Measurements).
- **Biospecimens**—Participants may be invited to provide biospecimens (blood, urine, and/or saliva) through their HPO or through a DV partner. Biospecimens will be assayed to generate various biological data, which may be incorporated into participants’ study records (see Section 7.4).
- **Passive mobile and digital health data (personal health technology data)**—Additional data may eventually be collected from a subset of participants to be determined, through health, wellness and fitness devices, other sensors, and/or mobile applications (see Section 7.2, Use of Personal Health Technologies).

Figure 3–1: Participant Interaction Flow



3.2 Making the Resource Accessible for Research

The *All of Us* Research Program aims to provide a useful resource that continues to be enriched and improved over time. The program expects to include detailed health and exposure information from participants over the lifespan of the program and retains the flexibility to enhance the program as funding allows.

A core dataset of all data contributed will be developed (see Section 11, Creation of the *All of Us* Research Program Resource). Ideally, in time, the core dataset will include PPI, physical measurements, baseline biospecimen assays, and baseline health information derived from EHRs from most participants. Data elements will be transferred through encrypted channels to the core dataset, which will be stored in the *All of Us* Research Program Data and Research Center (DRC). The data will be stored in a secure cloud-computing environment that follows rigorous standards to protect individual privacy and data confidentiality. The data can be queried through a dedicated analysis platform, the *All of Us* Research Program Research Portal, for research purposes. The DRC will develop tools to enable analysis of the data within this secure cloud-computing environment. Qualified researchers who wish to access the data will agree to not remove data from the Research Portal without approval. The *All of Us* Research Program will bring analysts to the data rather than the data to the analyst. An *All of Us* Resource Access Committee (AURAC) will serve as the stewards of the data.

3.3 Study Timeline/Study Duration

The *All of Us* Research Program is expected to last at least 10 years, with active enrollment occurring in the first 5 years. Follow-up is expected to be continuous for the life of the project. For example, data from EHRs will be added to a participant's *All of Us* dataset at least biannually for those participants who have consented to the EHR/Part 2 consent supplement ([Appendix: HIPAA Authorization for Research: EHR/Part 2 Supplement](#)). Participants will not receive notification each time their EHR data is added.

Lastly, the data analysis platform (*All of Us* Research Program Research Portal) will be built and available for use by qualified researchers within the second year and available for the life of the project.

4. Selection of Participants

The full potential of the *All of Us* Research Program will be realized only by capturing the full diversity of the United States regarding demographics (age, race or ethnicity, socioeconomic status), health status (both healthy participants and those with disease), and geography.

4.1 Eligibility

All individuals living in the United States or a territory of the United States are eligible to participate, provided they meet the inclusion/exclusion criteria below.

The program will actively recruit minority populations, such as ethnic, sexual, and gender minorities. This is an effort to enable rigorous research that may inform policy, prevention, and/or treatment approaches and thereby decrease current health disparities.

While the aim of the *All of Us* Research Program is to engage and enroll participants from all life stages, initial enrollment efforts will target individuals age 18 and older who are affiliated with a participating HPO or who are engaged DVs.

Educational content and consent materials will be available in English and Spanish at launch, with Mandarin Chinese planned for release rapidly thereafter. Therefore, initial enrollment efforts will focus on participants who understand either English or Spanish. The *All of Us* Research Program explicitly values inclusion (Section 2.1, What Is the *All of Us* Research Program?); as such, in the future, we will separately submit materials translated in other core languages reflective of the broader United States population for IRB approval.

Please also note that eligibility for inclusion of adults only is based on initial enrollment efforts to target adults 18 years and older. Any considerations to include populations younger than 18 years will be addressed in future protocol amendments.

Additionally, we will ensure participation is open to persons living with physical disabilities. Site-specific accommodations will be made by the DV sites and HPO sites to ensure that persons living with physical disabilities who meet the inclusion criteria are able to enroll.

4.2 Inclusion/Exclusion Criteria

4.2.1 Inclusion Criteria

- Adults 18 and older with decisional capacity to consent.
- Currently residing in the United States or a territory of the United States.

4.2.2 Exclusion Criteria

- Prisoners at the time of enrollment.

We do not intend to enroll prisoners without appropriate oversight by the IRB; however, we recognize that it is possible, even likely, that some participants may become incarcerated over the course of their participation in the *All of Us* Research Program. We believe that prisoners should neither bear an unfair share of the burden of participating in research, nor should they be excluded from its benefits, to the extent that voluntary participation is possible (Huang et al., 2017). Participation in the *All of Us* Research Program does not affect participants' rights and is in no way meant to change their social setting or impinge on prison resources or other inmates. Therefore, it is our intention to comply with all relevant applicable regulations under subpart C of 45 CFR part 46 for the inclusion of prisoners.

Until further notice from the IRB, the program material will include a note that people who are incarcerated cannot take part at this time but that we hope this will change in the future.

4.3 Vulnerable Populations

It is the goal of the *All of Us* Research Program to be as inclusive as possible. Although all vulnerable populations should be considered for enrollment, it is crucial that adequate consenting procedures be in place to ensure that the rights, safety, and welfare of those enrolled are not compromised.

The vulnerable populations that will be excluded in the initial enrollment efforts are summarized in Table 4–1: Vulnerable Populations Excluded at Launch. The *All of Us* Research Program is committed to ensuring that proper safeguards are in place to protect the rights and safety of all participants in the program. Separate protocol amendments will be developed that include plans to enroll vulnerable participants, such as children, prisoners, and cognitively impaired individuals. We look forward to working with the IRB to ensure compliance with the 45 CFR 46 and NIH OHRP (Office for Human Research Protections) guidelines to enable participation of vulnerable populations.

Table 4–1: Vulnerable Populations Excluded at Launch

Excluded at Launch	Vulnerable Population
X	Adults unable to consent
X	Children (<18 years old)
X	Prisoners at time of enrollment

Due to the minimal risk nature of this protocol, if an individual is interested and able to participate in the *All of Us* Research Program, and meets the eligibility criteria and is not specifically excluded, they will not be turned away. For example, adult women living in the United States or a territory of the United States who are capable of consent will not be turned away from participation based on their pregnancy status. If known, pregnancy status will be electronically recorded at the time of physical measurements.

5. Recruitment Outreach

To achieve the broad enrollment and participant diversity objectives of the *All of Us* Research Program, we will engage potential participants through a range of outreach approaches. Outreach is defined as all interactions that take place between the program and potential participants (i.e., in advance of program account creation). Potential participants will learn about the *All of Us* Research Program via:

1. Targeted advertisement, including:
 - Print brochures
 - Web advertisements
 - TV advertisements
 - Radio advertisements
2. Personal interest groups:
 - Social media
 - Community events
 - Press coverage
3. Directly at HPOs or DV sites, including:
 - In waiting areas
 - During the regular course of clinical care at HPOs
 - Local informational events
 - Regional informational events organized by program awardees, HPOs, or DV sites
 - Employee invitations

- Re-contact of consented participants in existing research programs

Potential participants who would like to learn more about the program will be directed to:

- Trained program staff at HPO and DV sites
- The *All of Us* Research Program Support Center
- The *All of Us* Research Program website (<http://joinallofus.org>)

Web-based materials will be especially important, given the broad geographic scope and the large numbers of prospective participants needing to be engaged to meet the one million or more enrollment goal.

Information materials targeted to the general public will be available on the *All of Us* Research Program website, including:

- Branding videos about the program
- Anthem video with or without English or Spanish subtitles
- Community video
- Frequently asked questions
- Messages from program leadership (e.g., the master narrative)
- Testimonials from participants (to be submitted to the IRB through subsequent submissions)

5.1 Outreach to HPO Members

HPOs may use both nationally and locally developed outreach approaches to engage their patient population. HPOs will be able to use approved program advertising materials as is or co-brand these materials following guidelines (images; look and feel). They may also use locally developed outreach materials that speaks to their local community. All locally developed outreach materials will be presented to the IRB as part of the Institution-Specific IRB Application (ISIA) process. Potential HPO participants will be provided with contact information for trained program staff via email or phone, listed on the advertisement, or interested parties can follow the link to the program website or mobile application for more information.

5.2 Outreach to Direct Volunteers

To supplement the regional efforts of the HPOs, The Participant Center (TPC) will develop the strategies to engage direct volunteers. TPC team is led by Scripps Translational Science Institute (STSI) and supported by Walgreens, WebMD, the Blue Cross Blue Shield Association (BCBSA), the National Blood Collaborative, and others. TPC outreach efforts will use approved national advertising materials and a multipronged strategy for outreach to historically underrepresented populations in biomedical research:

- We will identify populations we want to recruit, such as those living in remote areas not serviced by one of the awardee HPOs, people with multiple chronic conditions, those who are sexual and gender minorities, those with lower educational attainment or income, and those with limited vision or hearing. Targeted outreach

materials will be developed to specifically serve these populations. All targeted outreach materials will be submitted to the IRB for approval.

- A Support Center will provide assistance on demand, via phone, chat, and email, 7 days a week between the hours of 7 a.m. and 10 p.m. ET, excluding federal holidays. Instructions for contacting the Support Center will be posted on the program website and on the participant portal. The Support Center phone number and email will be listed on marketing and promotional materials. Anyone can contact the Support Center; however, assistance will be limited to topics covered within the IRB-approved FAQs and Knowledge Base. No clinical guidance or advice will be given. The Support Center will initially assist in both English and Spanish. All inbound requests will be tracked via an electronic ticketing system to ensure proper escalation and closure, auditing, measurement, and process improvement. We will use this tracking system to prioritize and develop new FAQs and Knowledge Base entries to ensure we are meeting the needs of participants.

The Support Center will record whether the caller is part of an HPO or a DV, the nature of the question or request, and the status of the request in order to ensure it has been adequately addressed. Callers will have the option to voluntarily provide their name, email address or a preferred phone number, and their state of residence for follow-up.

The Support Center staff will triage requests as follows:

- Tier 1—Handled by Support Center staff using the IRB-approved FAQs and/or Knowledge Base
- Tier 2—Directed to affiliated enrollment sites (HPO or DV) for site-specific response—for example, scheduling blood draws and physical measurements
- Tier 3—Directed to Vibrent for technical topics not addressed in the IRB-approved FAQs and/or Knowledge Base (e.g., technical problems with the website or mobile application)
- Tier 4—Directed to Scripps for topics that are not yet covered in the IRB-approved FAQs and/or Knowledge Base. Tier 4 tickets may include:
 - a. “Escalated issues” that were not satisfactorily responded to via the Support Center supervisor
 - b. Feedback or suggestions (program-related, marketing, research, technological, etc.)
 - c. New topics that should be added to either the Support Center Knowledge Base and/or added to the FAQs following IRB review and approval

For Tier 3 and Tier 4 topics, subject matter experts (SMEs) will be called for consultation as needed. These topics will be added to the Knowledge Base. Where applicable, responses may also be added to the FAQs, following IRB review and approval.

Standard quality monitoring will be performed to ensure proper escalation, auditing, measurement, and process improvement.

In the future, we will explore whether the Support Center can facilitate the enrollment process for future participants lacking digital access or acumen.

5.3 Outreach to Communities

We will deploy a mobile engagement asset (MEA) to bring awareness about the program to remote areas and geographic locations whose residents are traditionally underrepresented in biomedical research. By bringing information about the *All of Us* Research Program directly to these populations, we aim to break down barriers to equitable representation within the program. This outreach will be especially valuable for engaging highly mobile populations like migrant workers and those living in shelters and other temporary housing, racial and ethnic minorities, and the LGBTQ and disability communities. The MEA will offer personal exploratory interaction with the *All of Us* Research Program; special attention will be given to creating a warm and welcoming, but not coercive, environment where people can learn about the program. The MEA experience will be carefully developed to be considerate of cultural aspects and to leverage existing community network relationships. The MEA is an agile tool that can be leveraged for other uses when not scheduled for outreach to underrepresented populations. Other uses include support of HPOs and DV partner activity. Community and faith-based groups, consortium members, and other partners can request the MEA through an online event request form.

6. Enrollment

Enrollment in the *All of Us* Research Program is voluntary and not time-sensitive.

We will track participant enrollment level over time and report back to the Steering Committee and NIH on our success against ongoing targets for diversity and inclusion in the program.

6.1 Levels of Enrollment

- **Interested party or interested individual:**
 - Unregistered interested party: someone who has provided their email address to receive program updates, has downloaded the program app, and/or has pressed “Join Now” on the website.
 - Registered interested party: a person who has created an account by entering their name and email address and has chosen a language preference but has not yet completed the informed consent process.
- **Member:** a person who meets the eligibility and inclusion criteria who has completed the primary informed consent process. Has not yet participated in any program activities.
- **Participant:** a member who has participated in one or more program activities (questionnaires, physical measurements, provided biospecimen, EHR/Part 2 access, etc.)

6.2 Readability of Enrollment Materials

The Program has developed electronic enrollment materials. Consistent with best practice recommendations of the National Quality Forum (NQF) and the Agency for Healthcare Research and Quality (AHRQ) for engaging participants with a broad spectrum of health literacy, enrollment materials have been written at the middle-school-grade reading level. This ensures that these materials are broadly comprehensible by the greatest number of residents of the United States.

All public program copy was reviewed by reading level experts using both the Flesch Reading Ease and the Flesch–Kincaid Grade Level scales. Materials were further reviewed for sentences per paragraph; words per sentence; overall word, sentence, and paragraph counts; and use of passive voice. By adjusting the vocabulary used and the length and structure of sentences and paragraphs, reviewers worked to increase reading ease and reduce grade level. Whenever possible, copy was reduced in volume while retaining appropriate sentence structure (e.g., no single-word sentences). Finally, reviewers converted copy to the active voice to increase its accessibility and ability to engage low-literacy readers. Following analysis, program copy was re-reviewed to ensure that essential meaning and concepts were fully retained.

Further, where possible, the enrollment materials incorporate multimodality presentation methods (aural, visual, and interactive) to aid comprehension of persons with low literacy. For example, animated videos with visual cues and voice modulation will further facilitate comprehension in low-literacy populations.

Individuals can access enrollment materials through the program website or app. Recognizing that individuals may or may not have their own device for accessing these materials, examples of enrollment devices are listed in Table 6–1: Enrollment Devices.

Paper-based and telephone-based enrollment procedures will be developed following initial launch. These materials will serve those with low technology proficiency and/or without access to an online infrastructure and/or other preference or challenge that prohibits enrollment via the electronic process. These materials will mirror the approved text from the electronic consent process, although the ability to adapt and retain multimodality presentation approaches may be limited.

Table 6–1: Enrollment Devices

	At HPO site (+/- trained program staff assistance)	DV (+/- trained program staff assistance)
Participant device (wireless laptop, tablet, or smartphone)	Yes Using secure HPO site WiFi connectivity or participant-provided cellular internet	Yes Using DV site WiFi connectivity, participant-provided connectivity, or participant cellular internet
Participant device (wired, stationary desktop)	No	Yes Using Participant-provided connectivity or cellular internet
Site device (wireless)	Yes Using secure HPO site WiFi connectivity	Yes* Using DV site WiFi connectivity
Site device (wired, stationary computer or tablet installed in kiosk)	Yes Using secure HPO site WiFi connectivity	Yes* Using DV site WiFi connectivity

* Only for DV partners enabled to facilitate enrollment.

6.3 Account Creation

Account creation begins with the interested party clicking the “Join Now” button on the website or mobile application. Account creation requires the interested party to enter their first and last name and an email address or phone number, create a password and confirm it, and choose a preferred language from a drop-down menu.

This contact information will be stored securely in the Raw Data Repository, like other information containing personal identifiers. Access to personal identifiers will be available only to a select number of trained program staff for data validation and regulatory purposes. The DRC will then generate an internal study identification code, represented as an alphanumeric string that is used to access participant information without use of explicit personal identifiers.

Individuals must create their account themselves but can do so with the assistance of trained program staff either by phone through the Support Center or in person at an HPO or a DV partner site. At first, all individuals will create their account electronically. We recognize this limits participation by some individuals and could impact diversity and inclusion within some communities. A plan to accommodate individuals with differing levels of technological capability is to be developed and subsequently submitted to the IRB.

Accounts can be created using the web application interface or through the dedicated mobile application. The web application will be compatible with modern major browsers

and will include the full complement of educational material regarding the program, including the informed consent documents; individuals will not need to create an account to view this material. The mobile application will be available free of charge for iOS operating systems within the Apple App Store and for Android operating system on the Google Play marketplace. Prior to download, individuals may review information about the program posted on the Apple App Store and Google Play marketplace. After download, individuals can review educational content about the program within the mobile application without creating an account. *All of Us* Research Program educational materials, including informed consent forms, will be freely available and will not be limited by account creation on either the web or mobile application.

6.4 Information Collected Prior to Informed Consent

In addition to account creation, persons wishing to complete the consent process for *All of Us* Research Program through the web or mobile program application will be asked the following questions in advance of providing informed consent:

- They will be asked to confirm they meet each of the eligibility criteria (e.g., Are you age 18 or older?)
- They will be asked their state of residence. This enables compliance with state-specific requirements, such as disclosure of the California Experimental Bill of Rights (Appendices: [Primary eConsent Screens](#) and [California Experimental Subject's Bill of Rights](#)) to individuals residing in California.
- They will be asked if they are a member of any of the program affiliates within their state of residence. This enables customization of the app based on HPOs' readiness and preferences.

This information will be collected and used for the purposes described above.

6.5 Informed Consent Overview

All persons wishing to participate in the *All of Us* Research Program will complete an informed consent process (Appendix: Primary eConsent Screens). Through this process, participants will unambiguously indicate their consent to join, using IRB-approved text and visual aids (including video). The materials presented will be consistent across the program regardless of an individual's geographic location, enrollment method, or affiliation (DV or HPO).

The informed consent process will initially be administered and documented electronically. It is designed as a living process, with information loops and opportunities for periodic updates. Interested individuals will be able to access consent materials either by downloading the *All of Us* Research Program mobile app to their iOS or Android phone/tablet or through the *All of Us* Research Program website. The consent process is self-paced, and there is no time limit to complete it. It can be experienced as a self-navigated, staff-supported, or hybrid process. Individuals will be able to choose their preferred informed consent experience by (a) self-navigating the consent process through the web or mobile program application, (b) soliciting support from trained program staff at either an HPO or a DV partner site, or (c) calling the Support Center. We anticipate that HPOs may encourage a staff-supported approach and that DV partners, other than those

that can facilitate enrollment, may encourage a self-navigated model; ultimately, individual preference will determine the approach taken for consent.

Only trained Program Staff will be able to offer support to individuals with technical/computer issues, literacy issues, and/or interpretation of questions, during the consent process and beyond. This approach helps to ensure consistency among enrolling centers, as well as ensuring that an individual's decisional autonomy is respected.

Informed consent materials will be available in English and Spanish at launch and in additional languages thereafter. Translation of informed consent material into additional languages will follow launch and will be submitted to the IRB for review for equivalency and approval through an amendment/s process. Verbal translation into languages without official translation will not be allowed.

Any awardee institution wishing to use approaches to informed consent other than those described here will submit their site-specific plans to the IRB as part of the Institution-Specific IRB Application process.

6.5.1 Considerations for On-Site Enrollment

Individuals who are enrolled through an HPO and DV partner will be provided information on how to download the mobile app and/or website (see screenshots in Appendix: Primary eConsent Screens). An on-site kiosk or tablet/iPad may be available at some locations to review the eConsent and audiovisual content. If applicable, site-specific procedures will be submitted to the IRB as part of the Institution-Specific IRB Application (ISIA).

Interested individuals will be clearly informed that their decision to participate in the Program will not impact the care they will receive at either an HPO or from a DV partner. Program Staff will be trained to approach only individuals who are stable, coherent, and able to carry on a conversation freely. Anyone will be able to access the full complement of *All of Us* Research Program educational material, including the informed consent documents, through the web application, mobile application, and/or through the Support Center without required registration of any kind.

6.5.2 Paper-Based Consent

As a near-term alternative to the entirely electronic process, a paper-based consent process will be developed. Individuals will be required to register through the mobile application (app) or program website with their email address or phone number before paper consent can be completed. This can be accomplished with the help of trained program staff using on-site computers and/or mobile technology. For those using paper to provide informed consent, they will be provided with paper documentation of the phone number and/or email address that was used to register their account.

6.5.3 Fully Facilitated Consent

As previously described, the consent process may be self-navigated or completed with staff support. There are circumstances where a completely staff-facilitated consent process may be utilized, depending on the participant's physical, social, educational, or other limitations or preferences that necessitate this approach to meeting their needs as an

individual. Trained program staff experienced in facilitating standard informed consent procedures will be available to facilitate review of consent materials with individuals in such cases. Trained program staff members will utilize approved electronic consent visual aids and text during this process and will engage the participant in an informed consent discussion to answer any additional questions or concerns a participant may have.

Once the Support Center is ready, they will also have a standardized procedure for a fully facilitated consent process; a separate amendment will be submitted for IRB approval at that time.

6.6 Electronic Consent

An electronic informed consent process is to be used for all *All of Us* Research Program participants (at HPOs or DV partner sites) to ensure consistency and standardize consent information. This strategy was also selected to allow for rapid scaling of consent. The electronic consent process serves as an aid to understanding of the core elements of the Research Program. It includes information on the detailed nature, purpose, procedures, benefits, and risks of and alternatives to participating in the *All of Us* Research Program. It is available via the web and mobile applications.

Due to the longitudinal nature of the study, and to provide flexibility in the approach to consent, informed consent for the *All of Us* Research Program is modular. There are three consent modules (a primary module and two supplements), each of which requires an electronic signature from the Participant:

1. *Primary module*: The primary consent module gives an overview of all study activities. A signature on the primary consent form documents consent for participation in the PPI, Data Linkage, Physical Measurements, Biospecimen Collection, and Sensor/Wearable Technology (when developed) activities.
2. *HIPAA Authorization—EHR/Part 2 module*: The HIPAA Authorization—EHR/Part 2 module gives detail about allowing the program access to participants' electronic health records, including health records protected by 42 CFR Part 2 (drug and alcohol abuse patient records), hereafter referred to as "Part 2" records.
3. *Genetic/genomic analysis module*: The genetic/genomic analysis module will give detail about the genetic/genomic analyses that, with participant permission, will be run on participant samples and the return of genetic/genomics results. This module is still in development.

Each consent module is comprised of three information-giving components:

1. eConsent screens
2. Form requiring electronic signature
3. Formative evaluation

The electronic consent was designed to enable flexibility in arranging these components to meet the needs of member organizations with local populations in various states of readiness, while also providing consistent, multimodal informing content to participants.

Following a description of each of these information-giving components, we present several potential workflows that enrollment sites will be able to choose from.

6.6.1 eConsent Screens

The eConsent screens present key ethical concepts through a set of visual icons, short videos, and concise, highly structured text blocks (Appendix: Primary eConsent Screens). The development of the eConsent screens is informed by electronic consent design literature and formatting principles. These formatting principles aim to deepen participant attention and facilitate comprehension throughout the informed consent process, especially for participants who are self-administering consent.

Examples include:

- Focus on the essential:
 - Create a narrative focused on the most salient information
 - Limit concepts to one per screen
 - Follow national plain language and health literacy guidance
- Organize content deliberately:
 - Prioritize key words/concepts presented on each screen
 - Employ multimodality (aural, visual, and kinesthetic—through tapping, swiping and selecting) presentation methods

The videos associated with the eConsent facilitate elaboration on key aspects of the program without increasing reader burden for those of low literacy or those who learn best from non-text-based presentation of information (See Appendix: [eConsent Video Script](#)). Ten brief audiovisual segments describe elements of program participation, such as answering health questions, being measured, or giving samples, as well as data sharing and privacy. Each segment will autoplay upon the participant navigating to the given eConsent screen. Participants will not be able to navigate forward until the segment is complete, thereby ensuring a more uniform informing experience for all participants.

Consistent with the design of the modular consent, there are three core eConsent screen sets:

- Primary eConsent screens—present an overview of the *All of Us* Research Program and information on all aspects of participation (i.e., PPI, data linkage, physical measurements, biospecimen collection, sensor/wearable technology, EHR/Part 2 data donation, genetic/genomic analysis). See Appendix: Primary eConsent Screens.
- EHR/Part 2 eConsent screens—present a more detailed look at EHR/Part 2 data donation, including scope, limits, risks, benefits. See Appendix: [HIPAA Authorization: EHR/Part 2 eConsent Screens](#).
- Genetic/genomic analysis eConsent screens—will present a more detailed look at genetic/genomic analysis, including scope, limits, risks, and benefits. [In preparation; not included in this protocol submission]

Additionally, to mitigate informedness decay over time, two eConsent “refresher loop” screen sets can be used. Currently, we have one of these:

- Physical measurement/biospecimen refresher eConsent screens—for participants for whom physical measurement/biospecimen donation is separated in time from the primary eConsent, this refresher will remind participants of the scope, limits, risks, and benefits of these procedures. See Appendix: [Physical Measurement/Biosample eConsent Refresher Loop](#).

6.6.2 Consent Form and Supplements Requiring Electronic Signature

To meet regulatory requirements, a primary informed consent form ([Appendix: Primary Informed Consent Form](#)) and a supplement EHR/Part 2 form have been drafted. Another supplement about genetic/genomic analysis will be developed. These forms will be readily available for review through the *All of Us* Research Program website and through the app without any registration for access. Each form will be presented to participants following the related eConsent screen set. Participants will electronically sign these forms and receive an emailed PDF version of their signed consent document either electronically by email or in printed form from program staff at the time of an in-person visit to an HPO or DV partner, for individuals without an email address.

The signature at the end of the primary consent form indicates that the participant is consenting to PPI and data linkage. Additionally, this form documents consent for physical measurements, biospecimen collection, and sensor or wearable technology data collection, should the participant be invited and choose to participate in those modules of the *All of Us* Research Program; signature on any consent document does not constitute a “contract” of promised data donation by the participant nor that the program will ask for the data from the participant.

Signature on the EHR/Part 2 supplement consent form is required for release of electronic health records and Part 2 health record data. Another signed consent supplement will be required to authorize genetic/genomic analysis of donated biospecimens. This consent supplement form for genetic/genomic analysis is currently under development and will undergo legal review for compliance with the diverse state regulations governing genetic/genomic analysis for research prior to submission to the IRB. Participants may be required to sign additional documents (e.g., Appendix: California Experimental Subject’s Bill of Rights), as mandated by law.

Because the primary consent form and any supplement will contain personal identifiers, they will be kept separate from the data in the Program Research Portal that will be queried and analyzed by researchers. The signed consent forms’ data will be stored in the participant portal database, and copies of the signed informed consent forms will be stored securely in the Raw Data Repository, like other forms containing personal identifiers. Access to this data will be available to trained program staff via HealthPro for management purposes and for data validation and regulatory purposes.

6.6.3 Formative Evaluations

At the end of the primary, EHR/Part 2, and genetic/genomic analysis eConsent screens, and after viewing the related consent forms, participants will be required to complete a

brief formative evaluation prior to being able to electronically sign the consent form and thereby complete a consenting interaction. A formative approach was chosen to reinforce key concepts and specifically target common misconceptions in human subjects research (e.g., therapeutic misconception).

As individuals answer questions within the formative evaluation, they will receive immediate feedback on whether they have answered correctly or incorrectly. An educational reinforcing screen will be presented back to all individuals, regardless of correct or incorrect response. Individuals answering incorrectly will not be penalized. If a question has been answered incorrectly, participants will have the option to obtain contact information for assistance or to navigate onward. For participants enrolling at an HPO or DV partner site, the option to ask trained program staff for assistance will also be available. This formative approach supports participant informedness prior to consent and serves as a check on participant understanding, especially for participants self-administering consent.

6.6.4 Modularity of Consent Materials

Each of the three consent modules (primary, EHR/Part 2, genetic/genomic analysis) is composed of information-giving elements: eConsents, forms requiring signature, and formative evaluations. The consent framework has been designed to be modular to accommodate site-specific preferences and needs. We present six possible electronic consent workflows below. HPO and DV enrollment sites will select among these workflows for consent hosted in part or entirely on site. Finally, we present the self-paced, self-administered consent workflow that can be used by DVs and potentially for HPO volunteers if the HPO elects.

Options for organizing and navigating the primary consent module and supplement modules (EHR/Part 2 and genetic/genomic analysis) in one or in multiple sittings are presented in Figure 6–1, Figure 6–2, and Figure 6–3.

Figure 6–1: Options for Navigating the Consent Modules in One Sitting

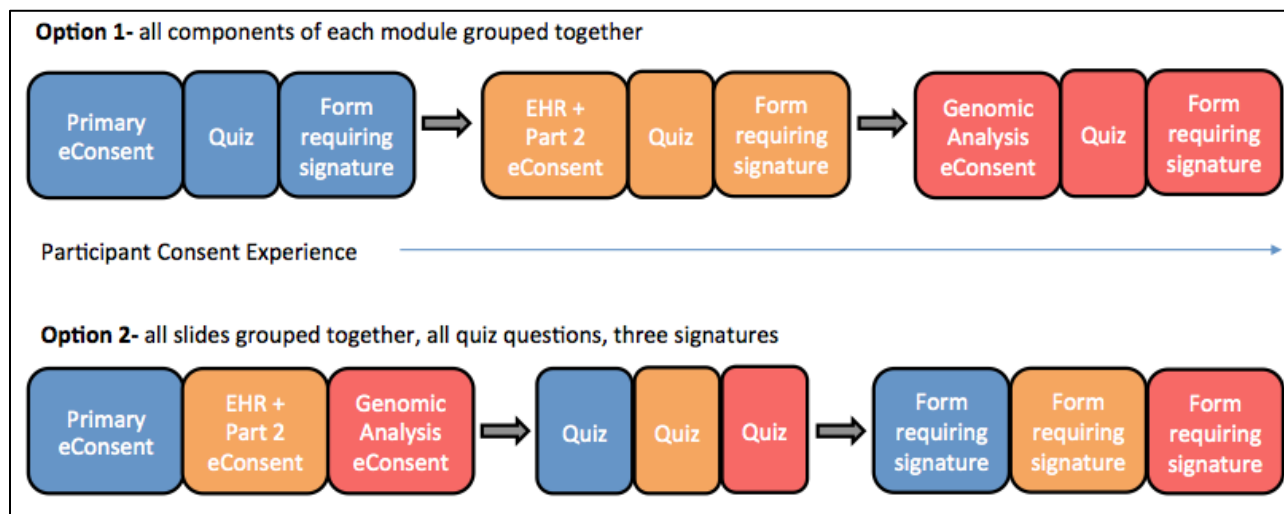


Figure 6–2: Options for Navigating the Consent Modules in More than One Sitting

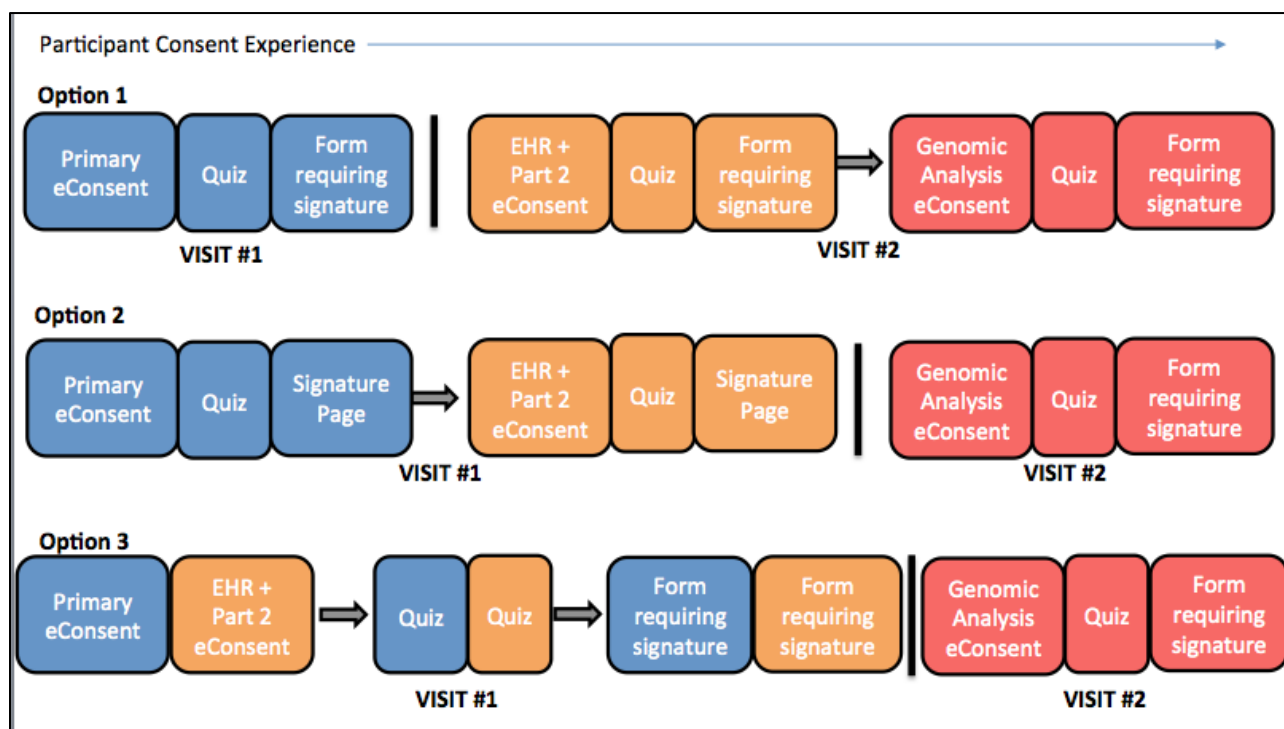
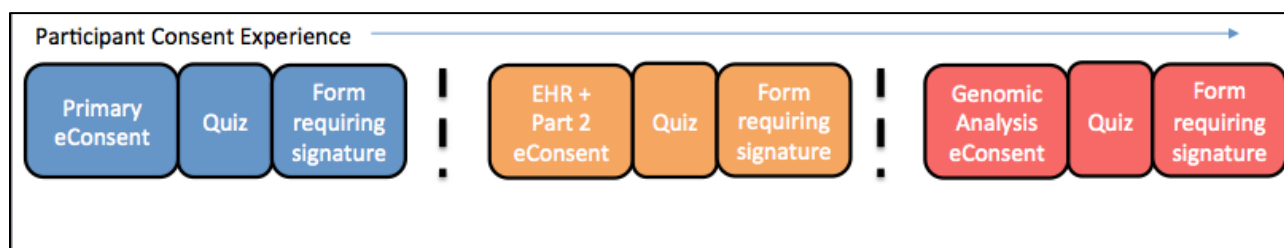


Figure 6–3: Self-Paced Self-Administration of the Consent Modules



6.6.5 Additional Consent Materials

Due to the longitudinal nature of the study, and to recognize that informed consent is not a discrete process but a long-term engagement between participants and researchers, we will deploy “refresher loops” to guard against informedness decay. These refresher loops will be eConsent screens designed to reinforce key concepts, especially for program activities that may be separated in time from the primary consent module. A physical measurement/biospecimen refresher loop is included with this submission (Appendix: Physical Measurement/Biosample eConsent Refresher Loop). A sensor/wearable technology refresher loop is planned and will be submitted to the IRB for review in a future amendment. Additional refresher loops will be developed, submitted for review, and deployed over time, depending on program and participant needs.

6.7 Additional Considerations

There may be site-specific implementation differences, such as languages used, interpretation services, cultural preferences for destruction of samples, etc.

Accommodation of these issues is critical to recruiting and retaining a diverse membership in the program. As and when these arise, an Institution-Specific IRB Application will be submitted to the IRB.

6.8 Data Oversight and Choice of Law

The large number of distinct state laws and regulations governing the collection and use of various data types targeted by the program have prompted the *All of Us* Research Program to seek guidance from the NIH Office of General Counsel and the Office of Civil Rights. These offices will provide recommendations on the appropriate application of state regulation in the context of this national program. This consultation is especially important given the long duration of the study, along with the well-documented mobility of the United States population and, specifically, the higher mobility of those who are poor and non-white (U.S. Census Bureau CB 16-189). Further, the program will target populations traditionally underrepresented in biomedical research who have exceptionally high mobility, including migrant workers, the homeless, and gender and sexual minorities. Creating a plan informed by understanding of these state-by-state variations will be essential to meeting our ethical obligations to mobile populations. The program will use this guidance in revisions to participant materials, consent, and workflow for all future submissions.

7. What Is Involved? Program Procedures

Once an individual has confirmed their decision to join the *All of Us* Research Program by completing the informed consent process, that person is a member and is eligible to start contributing information to the program.

Although some participants may complete the consent process and one or more PPI questionnaires online prior to coming to an HPO or DV site, trained program staff will follow site-specific policies and procedures to confirm the participant's identity (confirmation of name and contact information, photo ID, etc.) at the beginning of their appointment and that the participant wishes to move forward with study procedures listed in the consent document.

Initial program activities include enrollment and informed consent, as well as program activities that may follow this immediately. The anticipated time to complete the initial program activities and data collection for a participant who completes the entire process in one setting is about two hours (excluding time required for consent). As noted above, some participants may complete certain PPI modules ahead of time; therefore, the time required in one setting described in as listed below (Table 7–1: Estimated Duration of Program Activities) may be significantly less than two hours. These times are not intended to reflect time for transportation to the site or wait times prior to initiation of data collection.

Table 7–1: Estimated Duration of Program Activities

Domain	Description of Content	Duration
Enrollment	Create account via website or mobile application	2 minutes
Informed Consent	From website or mobile application:	Primary:

	<ul style="list-style-type: none"> • View primary eConsent screens • Review primary consent form • Complete primary formative evaluation • Sign primary consent form • As appropriate, view refresher loops and/or complete additional consent modules. 	10–20 minutes Additional informing content: 5–15 minutes
Participant-Provided Information	<ul style="list-style-type: none"> • Basics (sociodemographic information) • Overall health • Lifestyle (personal habits) • Personal health history • Medications • Family history • Health care access and utilization 	3–60 minutes (see below, Table 7–3)
Check-In	<ul style="list-style-type: none"> • Verify address/key personal information • Verify consent is e-signed before visit • Summarize what to expect of the visit; answer any questions • Instruct participant to remove bulky clothing 	5–10 minutes
Pre-Measurement Verifications	<ul style="list-style-type: none"> • Verify completion of PPI • Collect limited information relevant to the measurements/biospecimen collection (e.g., what time did the person last eat anything?) 	5–10 minutes
Physical Measurements	<ul style="list-style-type: none"> • Conduct program core physical measurements, to include: <ul style="list-style-type: none"> ○ Blood pressure and pulse—6 minutes ○ Height and weight—3 minutes ○ Hip and waist circumference—2 minutes • Re-dressing—5 minutes 	15–20 minutes
Biospecimen Collection	<ul style="list-style-type: none"> • Perform blood draw • Collect urine specimens • Collect saliva samples (instead of blood) 	10 minutes
Check-Out	<ul style="list-style-type: none"> • Verify the completion of measurements and biospecimen collection • Provide physical measurement data to the participant • Discuss what to expect post-visit; answer any questions 	5–10 minutes

7.1 Participant-Provided Information (PPI)

In addition to contact information and data for account creation, the program plans to obtain extensive information about a participant’s health status through self-completed surveys. This participant-provided information will include data relevant and necessary for scientific research studies (e.g., personal and family medical history, socioeconomic factors, and health care access and utilization).

Questions were selected, or modified, from various surveys previously validated in large cohorts and cross-sectional studies for collecting participant information related to health-focused research (e.g., the National Health and Nutrition Examination Survey [NHANES], the National Health Interview Survey [NHIS], the Behavioral Risk Factor Surveillance System [BRFSS], the Million Veteran Program, and UK Biobank). The questions have been further refined through qualitative testing during the pilot phase of the program, using

cognitive interviews and online user testing. The pilot also enabled exploration of survey understandability and accuracy of responses among members of diverse groups and the identification of gaps in survey coverage of issues important to participants.

7.1.1 PPI Readability Analysis

Consistent with the guiding principles of the program, reading analysis was completed on all participant-provided information (PPI) domain surveys to ensure they are broadly comprehensible by the greatest number of residents of the United States. All PPI domain survey questions were reviewed by reading-level experts, using the Flesch–Kincaid Grade Level scale. Questions were edited where needed to improve readability and clarity, in line with current best practices to use language at the fifth- to sixth-grade reading level. Additional directions and concept explanations were also added to complement question-and-response options as needed to improve clarity. Following readability analysis, module content was re-reviewed to ensure that essential meaning and concepts were fully retained.

Table 7–2: Readability Statistics for PPI Modules Designated for Use at Launch

Module	Flesch–Kincaid Grade Level
Basics	6.2
Lifestyle	5.9
Overall Health	7.1

The first three survey domains (Basics, Lifestyle, and Overall Health) were iteratively tested and refined using participant feedback. The questions included in each domain survey are presented in the Appendices: [PPI Survey Module: The Basics](#); [PPI Survey Module: Overall Health and Mental Health](#); and [PPI Survey Module: Lifestyle](#).

Prior to the physical measurements and biospecimen collection, participants must complete these three self-administered questionnaires (Basics, Lifestyle, and Overall Health). Participants will be able to save their answers and return to complete each survey later if needed. On average, it takes about 10 minutes at median and about 30 minutes at the longest to complete (Table 7–3: Survey Completion Times).

Table 7–3: Survey Completion Times

The <i>All of Us</i> Research Program Survey	Median (min:sec)	Range (min:sec)
Basics	6:30	2:00–17:51
Lifestyle	1.23	0:17–7:05
Overall Health	2:00	0:14–6:06

Pilot testing was primarily online, using a general survey format, and there were a limited number of participants with visual impairment who participated. It is recommended to use strategies and technology that cater to their needs.

Participants will be invited to answer additional survey questions about their health throughout the duration of their participation. For instance, surveys exploring other domains (Personal Health History, Medications, Family History, and Health Care Access) are currently being tested via cognitive interviews and will be submitted to the IRB for review and approval prior to implementation. Surveys in additional domains (e.g., Diet, Physical Activity, and Sleep) are planned. They will be developed on an ongoing basis and will be submitted to the IRB for review and approval prior to implementation.

7.2 Use of Personal Health Technologies

Data from sensors and software applications can enrich self-reported data on lifestyle and environment and could give researchers a clear view into these factors that have previously been difficult to capture with accuracy.

It is anticipated that, throughout the life of the program, an array of wireless sensor technologies will enable the collection of individual physiologic and environmental data not previously possible. Some of these sensors could include those already built into smartphones, such as those that can measure motion, activity level, and sound. Others will include wearable sensors including, but not limited to, wristbands and watches that currently can measure activity, sleep duration, heart rate, and respiration; however, in the future we anticipate will be able to monitor much more. Additional sensor technologies may include those placed within a participant's residence or automobile that can passively monitor environmental parameters such as temperature and air quality and track movement and sleep quality, as well as a variety of biometrics.

Passive data contribution via sensor technology will be supported within the *All of Us* Research Program. Many individuals across the United States already routinely utilize a variety of wearable and other wireless sensors. It is anticipated that participants will also be invited to provide the data from these devices to the program when available.

7.3 Physical Measurements

Participants will have a standardized set of physical measurements collected and recorded in HealthPro. The same core set of measurements will be carried out in participants in the *All of Us* Research Program irrespective of enrollment through an HPO or as a DV.

The inclusion and exclusion of specific measurements as part of the baseline physical measurements were determined based on their potential relevance to research, widespread reproducibility in all enrollment settings, the time and training requirements needed to carry them out appropriately, and the resources required to obtain them. In total, it is anticipated that the components to be included in the baseline physical measurements will require 15 to 20 minutes to complete.

In some circumstances, a home visit by a trained program staff member may be necessary to enable the physical measurements.

The physical measurements will include physiologic (e.g., blood pressure and heart rate) as well as anthropometric (e.g., height, weight, waist and hip circumference) measurements in all participants. Body mass index will be calculated automatically from

measured height and weight. Obtaining these physical measurements will confer minimal risk to study participants, as outlined in Section 8 (Risks/Benefits Assessment).

The information will be recorded on a dedicated HealthPro platform by the trained program staff member conducting the measurements. At the end of the physical measurements, participants will have access to their physical measurements almost instantaneously through the Participant Portal (web and mobile). In addition, participants may have the option to receive their physical measurements in writing before they leave the HPO/DV site.

Trained staff will be notified immediately upon entering of any measurements that are deemed actionable based on deviation from population norms in HealthPro. HealthPro will provide clear guidance to trained staff regarding next steps, including referral for additional evaluation. See Section 10 (Access to Individual-Level Information for Participants) for additional detail.

7.4 Biospecimen Collection

Understanding the relationships between circulating biomarkers or genetic variation as they relate to disease prevention is a primary aim of the *All of Us* Research Program. The objective of the program regarding biospecimens is to collect samples that would allow the broadest range of assays that could reasonably be envisioned for the future and to avoid collection, processing, or storage approaches that would inherently preclude such assays.

The Biobank will be responsible for working with the DRC and HPO/DV sites to develop and provide standard operating procedures and kits for the collection, initial processing, and transfer of the biospecimen to the Biobank. Participants will be asked to provide at the most 44.5 mL of blood and about 10 mL of urine. In cases where it may not be possible to obtain a blood sample, a saliva sample may be collected instead for the purposes of isolating DNA. For individuals who enroll via designated HPOs, biospecimen collection may occur at the initial enrollment visit, following consent and completion of the Basics PPI module. DVs will travel to a designated facility for biospecimen collection. In some circumstances, a home visit may be necessary to enable specimen collection (e.g., individuals who report limited mobility, whose health prevents commuting, and those who live in an area where there is no enrollment site within a reasonable distance).

7.4.1 Home Visit: Notice of Future Addendum to Program Protocol

Specific guidelines for accepting home visit requests from participants are being drafted. Those guidelines will be presented to the IRB before being implemented.

7.4.2 General Approach to Sample Collection

The Biobank procedures included in a separate Manual of Procedures specify the samples to be collected, the preprocessing requirements, shipping temperatures, the transport of samples to the Biobank, and the processing, aliquoting, and storage of each sample type.

For the blood collection:

1. The maximum number of needle sticks by the phlebotomist is three. If unsuccessful after the first two needle sticks, and only with the consent of the Participant, one additional attempt will be made, ideally with a new phlebotomist.
2. If the first collection attempt is not successful, the participant may schedule an additional visit to complete the biospecimen collection.
3. If the sample collection is not successful after two attempts, or if the participant is not able to return for a second visit, the phlebotomist will propose to collect a saliva sample for DNA.

Note that DNA will not be tested without explicit participant consent for genomic analysis in the genome consent module, which is still under development at this time. If the minimum blood draw of a 4 mL EDTA tube is successfully drawn, the blood draw will be considered successful and saliva will not be sought.

The participant's health and the total volume of blood drawn on any single day need to be considered. Recognizing that some participants could be recruited from outpatient HPO sites where other specimen collections may happen for standard of care, ambulatory participants who are healthy or in stable medical condition should not have more than 200 mL of blood drawn in a single day.

Table 7–4: Questions to Participants Prior to Blood Sample Collection

Question to ask participant	If answer is “yes”	If answer is “no”
In the past week have you donated blood (e.g., blood bank, Red Cross), platelets, or plasma?	Participant will need to reschedule their biospecimen collection at least 5 days past the initial donation date	Research specimen collection to occur as normal
In the past 6 months, have you had a blood transfusion?	Participant will need to reschedule their biospecimen collection at least 6 months past the initial date of blood transfusion	Research specimen collection to occur as normal

In order to address this issue, along with concerns around potential contamination, participants will be asked a series of questions pertaining to blood draw and transfusion at three distinct times: at the time of registration, during scheduling, and immediately prior to blood draw. Based on the participant's responses, trained program staff will then adhere to the procedures described in site-specific Policies and Procedures (Table 7–4: Questions to Participants Prior to Blood Sample Collection).

Additional potential risks to the participant are expected to be minimal, as outlined in Section 8 (Risks/Benefits Assessment).

7.4.3 Biological Samples to Be Collected from Participants

Types of sample collection tubes are detailed in Table 7–5: Sample Collection

7.5 Biospecimen Processing and Storage

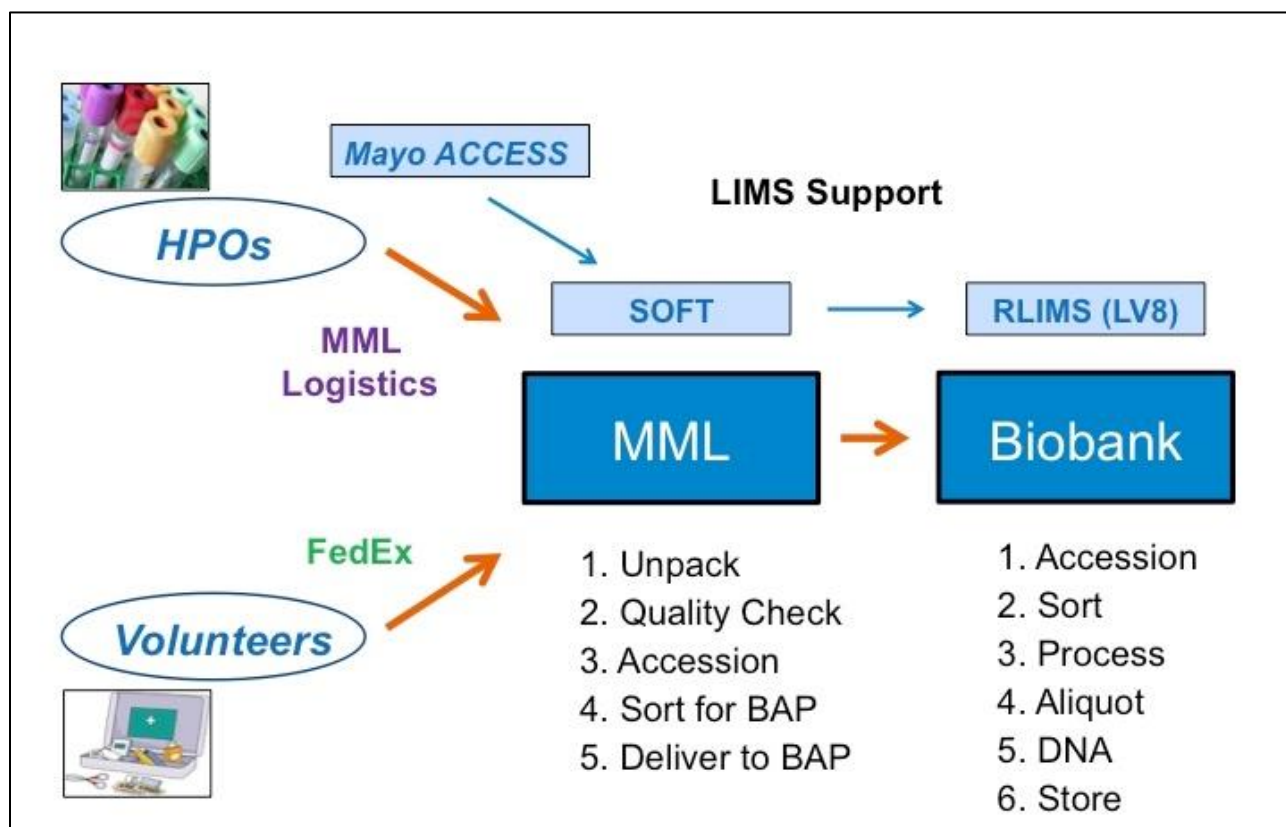
Biospecimens obtained through HPOs and DV sites will be shipped to Mayo Medical Laboratories (MML) for initial unpacking, accessioning, and sorting. They will be processed and stored in the centralized Biobank at Mayo Clinic. Samples will be held at the centralized Biobank indefinitely unless an individual participant withdraws from the study.

The centralized Biobank will be responsible for facilitating collection, shipment, processing, DNA isolation, sample aliquoting, storage, and future access to biospecimens. Initial sampling processing will be performed at the site of collection followed by a shipping protocol that maintains the cold chain needed to prevent specimen degradation.

Table 7–5: Sample Collection

Type of sample and collection tube	Volume collected (mL)	Transport (T°C)	Fraction and (number) of aliquots created	Aliquots –80°C	LN2
(1) Clot activator (SST)	8.5	4	(4) Serum	1.0 mL	—
(2) Plasma separator (PST)	8	4	(4) Plasma	1.0 mL	—
(3) Na-heparin	4	4	(2) WB (+DMSO)		1.0 mL
(4) EDTA	4	4	(2) DNA	0.5 mL	—
(5) EDTA	10	4	(5) Plasma (1) WBC (2) RBC (+glycerol)	1.0 mL	—
(6) EDTA	10	4	(5) Plasma (1) WBC (2) RBC (+glycerol)	1.0 mL	—
Urine	10	4	(6) Urine	1.0 mL	—
Saliva (backup)	2	4	(2) DNA	0.5 mL	—

Figure 7–1: Biospecimen Flowchart



Mayo ACCESS —This is proprietary software developed by Mayo Clinic to support sample accessioning at collection sites.

7.5.1 Processing Methodology

The collection site will perform minimal sample processing as described in the Biobank standard operating procedures. All specimens will be stored refrigerated until shipped. Specimens will be shipped to the Biobank within 24 hours of collection and processed by the Biobank within 40 hours. The shipment and processing timeline will be met in all circumstances, including holidays and weekends.

All blood tubes will be processed at the Biobank as described in the Biobank standard operating procedures with the products outlined in Table 7–5: Sample Collection. Information on all aliquots, including the volume for each, will be recorded in the laboratory information management system and linked to Biobank ID.

7.5.2 Transport of Biospecimens

All biospecimens will be shipped to Mayo Clinic in Styrofoam containers containing a cool pack to keep samples cool. For HPOs, a Mayo Medical Laboratories (MML) courier will be responsible for the packaging materials and containers, packing samples, and adding the

cool packs in the shipping container. The logistic capability provided by MML will be used to transport the specimens from the HPO to the Biobank. MML utilizes a network of couriers, coupled with a direct arrangement with FedEx and other carriers, to enable daily domestic and international specimen shipment from clients to the performing laboratories in Minnesota, ensuring that shipments are made in accordance with all federal, state, and international regulations. For DVs, a kit will be provided to all collection sites. The kit includes the supplies required for a complete blood draw and urine collection, including the Styrofoam container and a cool pack and shipping instructions. Completed kits will be shipped back to Mayo Clinic via FedEx courier.

7.5.3 Reliability of Sample Tracking and Identification

The collection sites will utilize MayoLINK to order the Participant's biospecimen collection, a Mayo Clinic application that provides connectivity to Mayo Medical Laboratories (MML). The Biobank laboratory information management is built on software developed by LabVantage Solutions, Inc. (www.labvantage.com). Core capabilities include kit tracking, sample accessioning and annotation, sample processing and testing, storage, and shipping. All aspects of the sample lifecycle are tracked. Security within this application is robust and multilayered to keep participant and sample data secure.

The enrollment sites will utilize HealthPro to record information from participants' physical measurements and to complete the biospecimen ordering workflow. Within HealthPro, authorized and trained program staff will be able to view the first name, last name, date of birth, and zip code of a participant to verify participant identity during the measurements and biospecimen collection. A unique Biobank ID will also be displayed. Prior to sample collection, a sample manifest and labels for the collection tubes will be printed via the HealthPro Portal. The collection tube labels will contain the unique Biobank ID but not other participant identifiers. The Biobank ID will be linked to the participant ID by the DRC. Security will meet Federal Information Systems Management Act (FISMA) Moderate Authorization and Accreditation standards.

7.5.4 Sample Receipt, Verification, and Routing

Samples will first be transported to MML. Trained Program Staff will triage incoming shipments by shipment time. Specimens will be taken from their original shipping containers and stabilized at the correct temperatures. The specimens will then be expedited to the internal operations area for order processing and receipt verification before being routed to the Biobank. Operators manage the automation and specimens receipt and processing. The validated transportation temperature is maintained at all times during pre-analytic processes, and specimens will be promptly delivered to the Biobank at the same temperature used for shipping.

7.5.5 Long-Term Specimen Storage

Processed blood samples will be stored in robotically controlled -80°C freezers, and whole blood samples will be stored in vapor phase liquid nitrogen units. Most prepared specimens will be stored at the primary site in Minnesota; the Jacksonville, Florida, Biobank facility will serve as the off-site, secondary storage site for approximately 25% of

the samples. Both Biobank sites have a comprehensive disaster recovery and business continuity plan.

7.5.6 Destruction of Biospecimens

Participants in the *All of Us* Research Program may withdraw from the program. In some cases, participants may wish to have stored biospecimens destroyed as part of this process. The procedure for destruction and disposal of biospecimens is outlined in Section 9.5, Destruction of Specimens).

7.6 **Electronic Health Records (EHRs)**

Through a consenting process, participants will be asked to authorize linkage of their EHR information if available. Although such linkage involves moderate risk to privacy and confidentiality (see Section 8.1, Risks), longitudinal tracking of health outcomes through EHRs is an important component of the *All of Us* Research Program.

EHR data may be sent directly by the participant's health care providers to the DRC or sent by the participant to the program through [Sync for Science](#). The majority of EHR data will likely be sent by HPOs in the near future, and certainly for the HPO participants. Access to EHR data will be repeated regularly throughout the life of the program. The initial data types to be included are demographics, visits, diagnoses, procedures, medications, laboratory tests, and vital signs, but may be expanded to all parts of the EHR, including health care provider notes. The feed may include mental health data, HIV status, substance abuse and alcohol data, and genomic information stored in the EHR. Participants may need to complete and sign a separate informed consent module to authorize access to their complete EHRs.

We will create an informatics infrastructure to clean and standardize data from disparate EHR systems across the United States; this broadly applicable system will be a key contribution of the *All of Us* Research Program to health informatics research efforts nationwide. For Participants enrolled by HPOs, the site will extract data from the participant's EHR, format it according to the DRC's data model (based on the Observational Medical Outcomes Partnership [OMOP] Common Data Model version 5 at www.OHDSI.org), and transfer it to the DRC using secure protocols.

Although obtaining EHR data from DVs presents unique challenges, early pilot studies have demonstrated feasibility of such an approach. For example, the [Sync for Science](#) (S4S) project launched by NIH and the Office of the National Coordinator for Health IT is creating a technology that aims to make it easy and safe for people to securely share their EHR data for research. S4S has been adopted by the *All of Us* Research Program and initially will be enabled in a small pilot for DV participants at S4S-enabled DV sites. *All of Us* Research Program DV participants who have enrolled at one of these pilot sites will be able to sign into their health care provider's patient portal using the S4S workflow and authorize sharing their EHR data with the program. Their health care provider's system will provide a secure application program interface (API), which is used by the research Program (rather than the provider sending data out) and transmitted to *All of Us*.

Important gaps in current methodologies include the ability to acquire EHR information from:

1. HPO enrollees who obtain some of their care outside of the HPO;
2. DVs who either do not have an EHR or possess an EHR that is not readily shareable.

We anticipate that capacity in these domains will improve over time.

7.7 Data Linkage

Linkage of diverse data streams may enhance the analyzable dataset from a given individual. The *All of Us* Research Program will obtain PPI data, EHR data, physical measurement data, and biospecimen data. Linking these data to additional data sources relevant to the individual may present a more complete picture of the health of the individual.

Most data linkages use common identifiers (e.g., first name, last name, date of birth) to uniquely associate information from various sources from a given person. Algorithms for deciding if one person is the same as another can be either deterministic (i.e., exact match) or probabilistic (likelihood of match). Use of identifiers in a human-readable form is referred to as “clear text” linkage method. Most current data linkages in health care are using clear text. Individual record linkage can also be achieved using record linkage methods to protect privacy—for example, using “hashed” identifiers for linkage. In this method, a person’s specific attributes are replaced with a unique code that cannot be reversed to yield the original identifiers.

7.7.1 Geolocation Data Linkage

An alternate means to link data to a participant is through home (i.e., residential) address or another location-based proxy. “Geocoding” of a participant to a specific geographic region enables inclusion of spatially dependent data, such as census, weather, or pollution data. We will build a geographic profile for participants who provide their residential and employment addresses through the PPI. All addresses will be prospectively geocoded into latitudes/longitudes. We will securely map addresses to geolocations through corresponding census tracts, block groups, and ZCTAs (ZIP code tabulation areas). Other data elements such as % urban/rural and population will be linked to participant geographic profiles.

A set of social, community, and environmental variables has been prioritized to populate an initial core linked dataset. This core set includes American Community Survey Census data, USDA (U.S. Department of Agriculture) Food Access Research Atlas, Environmental Protection Agency (EPA) outdoor air quality and air toxicity data, National Oceanic and Atmospheric Administration (NOAA) weather and climate data, and health care facilities information from the Area Health Resources File. Each of these datasets will be downloaded into the program’s secure environment (for their entire covered regions) and matched to participants, without sharing participant geolocations with these external entities. In time, more variables may be added to the core set as they are identified.

We will also investigate mapping in more complex environmental datasets from the EPA or

other resources, such as daily air particulate matter readings, which are not constrained to standardized formats and have varying frequency of data collection. Many of these data elements may require complex modeling and curation and would be included based on investigators' interest in such data. The DRC will facilitate the necessary linkages between the needs of investigators and the complex environmental data sources in order to generate relevant and interpretable datasets. Over time, these linkages may lead to methods or curation that will allow for complex environmental datasets to be considered "core" variables and thus available to all investigators.

No additional participant consent will be undertaken for these data linkages, as it is discussed in the primary consent.

7.7.2 Other Types of Data Linkage

Examples of data sources that may be valuable to link within the *All of Us* Research Program in the future include:

- Social Security Death Master File—The Social Security Administration generates a list of deceased people in the United States. Although in recent years updates to the file have been delayed, linkage to this file can identify people whose death is not documented within an EHR.
- Pharmacy system data—Pharmacies, pharmacy benefit managers, and health information networks often contain medication prescription and dispensation data beyond any single institution's EHRs. Early conversations with SureScripts, a health information network provider, revealed that SureScripts is under a Business Associate Agreement with institutions holding the original data and would need additional approval from participants to share data for linkage with the program. SureScripts does use an internal Master Patient Index for purposes of linkage and can use this for linkage with the *All of Us* Research Program data. A Master Patient Index is a database that tracks all the possible identities for individuals within a system.
- Claims data—Private and public payers collect service and payment data on care received that may span multiple care sites. These data may lack some clinical details, but often provide more broad coverage of the providers/procedures/costs associated with the care of the individual. Access to these data is often restricted and requires significant additional approvals and cost. Note that many insurers make some electronic claims data (e.g., Explanation of Benefits) available directly to patients, who can decide to share these downstream.
- Health registry data: Most states and territories require mandatory reporting of cancer cases to a central, non-public registry administered by the CDC. These data cover 96% of the United States population and may provide more detailed data related to cancer cases (e.g., tumor type or stage) than found within the EHR. Additionally, many sites also maintain cardiothoracic, device, and other registries. When available, we would seek to include health registry data in data uploads from HPOs or through obtaining other national health registries derived from clinical data.

While data linkage is encompassed in the participant consent, it is anticipated that prior to linking participant data with external sources, an amendment will be filed with the IRB for any linkages to "health registries" or "claims data" that require the DRC to share

participant-identifying information to an outside entity. Such submissions would detail the data to be linked and the general methods for doing so. No additional participant consent will be undertaken. The consent discusses that identifying information may be shared in this process.

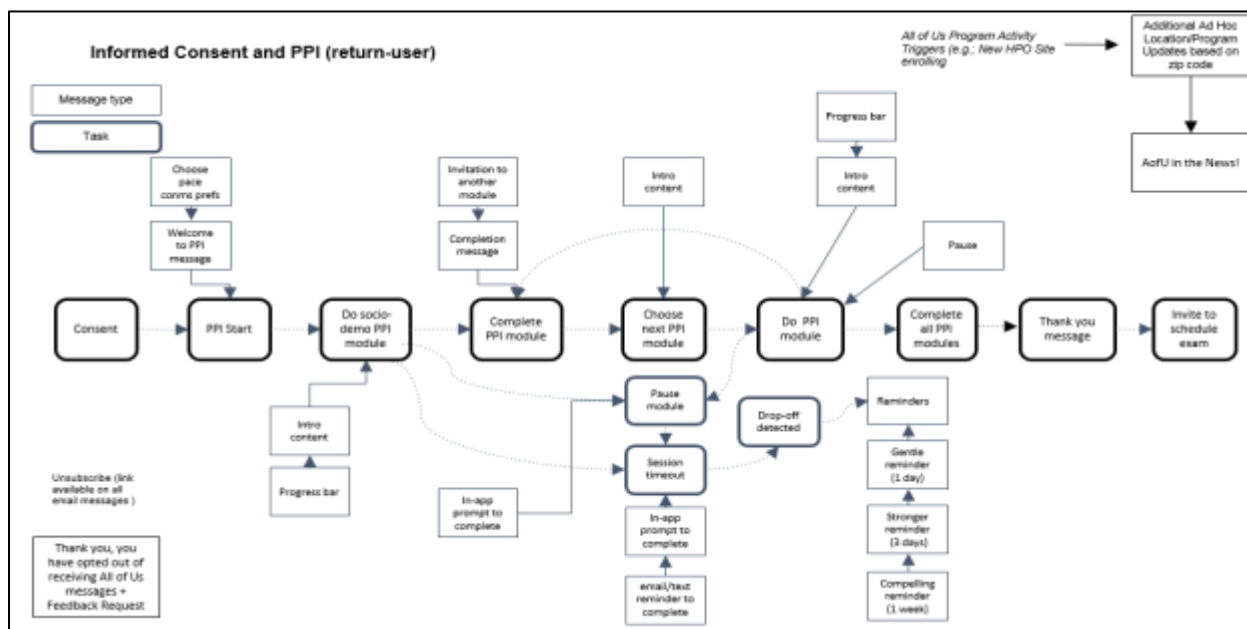
7.8 Early and Long-Term Participant Involvement

7.8.1 Early Communication Workflow

A communication workflow sample is provided to give IRB members a snapshot or “wireframe” of the business logic and strategies to keep our *All of Us* participants actively involved as they complete stages of the data collection process (see Figure 7–2: Data Workflow Sample for Participants).

The Participant Portal will deliver a message to the participant following successful consent. The transactional notification message sent post-consent will define the purpose and content of the PPI module. The message will also welcome the participant to start the first PPI module. If the participant is inactive for a certain amount of time while working on a started PPI module, the Participant Portal will generate a message informing the participant of the inactivity.

Figure 7–2: Data Workflow Sample for Participants



In contrast, if an individual has signed out without completing a started PPI module, a single message will be sent indicating a session timeout. User reminders will be sent out depending on completion status of PPI modules.

7.8.2 Long-Term Communication

The *All of Us* Research Program is designed to allow and encourage participants to remain actively involved for up to a decade, if not more. Following the collection of data at

enrollment through PPI, physical measurements, and collection of biospecimens, we will cultivate ongoing connection to the participant through the following two-way communication outreach strategies:

- Newly developed PPI modules to obtain new and updated health-related information annually.
- Encourage DV participants to connect their EHR data to the program using Sync for Science or other mechanisms on a regular basis to maintain timeliness of EHR data.
- Potentially targeted communications to gauge interest in exploring new studies that are part of the program for which the participant might be eligible—for example, studies of wearable sensors or specific genomic studies.
- Monthly, short, “health of a nation” snapshot questions or information designed to take no more than 2 or 3 minutes and provide participants with health and wellness information that would be of interest to them.

A central tenet of long-term involvement is that the participant will control both the frequency and method of communication from the program. For example, the participant can choose not to be informed of some types or all types of new studies or ask not to receive any of the monthly messages. Participants will also be able to unsubscribe to all future communications. Those who select this option would no longer be contacted directly or invited for follow-up procedures. This option would allow continued use of information and samples already provided and would still authorize further collection of electronic health record information from their automated database linkage.

Program communications will primarily be conducted electronically (e.g., email, in apps). Individuals who register with a phone number instead of an email address will be able to view a wall feed in the app or through the website, although there will also be capabilities for SMS (short message service) communications in the future. The need to develop paper and phone outreach processes for participants without email or mobile phones will be evaluated.

Participants will receive a message from the program up to every 30 days, alternating between a bimonthly newsletter and an invitation to engage in new educational modules. The newsletter will include program updates, such as new enrollment numbers, local events, or new findings. The educational modules will include citizen scientist modules with topics such as how to utilize program data and learning some of the basics about science. This content will be submitted to the IRB separately. There will also be the opportunity for participants to share personal reasons for joining the program, so that participants can learn more about why others have joined and what benefits they have experienced from the program.

8. Risks/Benefits Assessment

There may be risks, discomforts, and inconveniences associated with participation in research; these deserve careful scrutiny. This is not a medical treatment study. We do not expect any adverse medical events from participating, other than those listed below.

8.1 Risks

8.1.1 Loss of Privacy/Confidentiality

The primary risks are the potential loss of a participant's privacy and the loss of confidentiality of a participant's personal health information. These risks will increase as the study progresses and ongoing health information is collected.

8.1.1.1 *Privacy*

All data collection—including administration of questionnaires—will be conducted in a private room/area or in a location of the participant's own choosing, if they use the web/phone application.

8.1.1.2 *Confidentiality*

All directly identifiable information will be protected by systems meeting or exceeding the FISMA Moderate standards and authorized to operate by NIH and the NIH Office of the Chief Information Officer (OCIO). The HPO-owned devices used to register and collect participant information will be shut down automatically after a few minutes of non-use. Transmittal of information between sites also complies with high standards of security and is included under the review and approval purview of the NIH OCIO.

There is the risk that a third party may ask the *All of Us* Research Program to disclose information about participants without their permission as part of legal or other claims. The *All of Us* Research Program has obtained an [NIH Certificate of Confidentiality](#) to protect *All of Us* Research Program researchers from disclosing names or other [identifying characteristics](#) of participants in response to legal demands. This Certificate of Confidentiality covers all program activity, including the HPOs and DV sites, the program awardees, and vendors involved in the *All of Us* Research Program.

8.1.2 Physical Measurements

Participants may feel uncomfortable with some of the physical measurement procedures and/or results from those measurements. For example, participants will be asked to partially disrobe in order to allow for accurate measurements of weight and waist and hip circumference. These measurements themselves, plus others such as blood pressure and pulse, may lead to embarrassment or concern by participants. These procedures are standard medical procedures and pose no additional risk to participants other than their discomfort of potentially working with someone who is not their personal health care provider. In order to minimize these risks, all physical measurement procedures will be performed by trained program staff and will be carried out in the most respectful way possible. Participants will be reminded at the beginning of their physical measurements that they may opt out of some or all physical measurements without any impact on their ability to still participate in the program.

8.1.3 Participant-Provided Information (PPI)

Sensitive information may be revealed during the screening process and/or during the study. Completing the surveys or questionnaires may cause fatigue, frustration, anxiety, or boredom with the time it takes; participants will be reminded that they may take a break at any point. Completing the questionnaires may cause some people to feel emotional distress. All health survey questions will be optional; therefore, participants do not have to answer questions they do not want to.

8.1.4 Biospecimen Collection

Blood sampling risks include bruising of the arm and fainting. The modest amount of blood drawn should not have any adverse physiological effects, nor should it lead to any long-term distress. Risks for bloodborne pathogens from accidental needle sticks and during sample processing exist. With venipuncture, approximately 5% of people may faint, feel nauseous, or feel dizzy; a bruise may also form at the puncture site. The risk of a blood clot forming in the vein is about 1 in 100, while the risk of infection or significant blood loss is 1 in 1,000. Trained program staff will use standard sanitary biological specimen collection safety protocols for collection and processing of samples (e.g., antiseptics, gloves, and appropriate clothing). All objects that come in contact with bodily fluids will be disposed of in appropriate biohazard waste containers.

8.1.5 Access to Electronic Health Records

Throughout the program, trained program staff will access participant's EHR data. There is a risk of loss of confidentiality as described above. This will be further minimized through robust standard operating procedures regarding EHR access and abstraction. In addition, program staff will complete the required training regarding Human Subjects Ethics, the Health Insurance Portability and Accountability Act (HIPAA), Responsible Conduct of Research, and Good Clinical Practice as is appropriate for their role in the *All of Us* Research Program.

8.1.6 Participant Re-Contact

Participants will be re-contacted from time to time for follow-up. This may be annoying to participants over time; however, they will be reminded that their participation is voluntary and they do not have to participate in any procedures. Participants can choose the frequency with which they are contacted and can elect to stop all future contact.

8.1.7 Unknown Risks

Participants will be informed that the study may include risks that are currently unknown. When possible, the *All of Us* Research Program will inform the participant if new risks are identified that could affect their decision to participate.

8.1.8 Incidental Findings

The required physical measurements may uncover an abnormal value that may be actionable. See also Section 10.4 for procedures for managing emergent and urgent

medically actionable findings. Participants may experience stress as a direct result of receiving health findings/measurements that may be indications of illness. Cost for emergency services and/or follow-up care will be the responsibility of participants. The *All of Us* Research Program does not assume responsibility for fees associated with responding to any emergent or urgent situations both for medical care or transportation.

8.2 Benefits

The *All of Us* Research Program has potential societal benefits as a robust research resource that can facilitate the exploration of biological, clinical, social, and environmental determinants of health and disease. The program aims to enroll one million or more participants across diverse populations from across the United States to provide insight into the substantial inter-individual differences in physiology, risk of disease, and response to therapy. The information and biospecimens collected will become a useful resource for researchers to investigate why some people develop certain health conditions while others do not. The *All of Us* Research Program invites participants to become partners in the data gathering and research process through various means, including through data return and as citizen scientists investigating the data. Substantive participant involvement will occur at all levels of the *All of Us* Research Program including oversight, design, implementation, and evaluation. The combination of a highly-engaged participant population and rich biological, health, behavioral, and environmental data will provide a key resource for biomedical investigation capable of ushering in a new and more effective era of American healthcare.

We anticipate that the societal benefits stemming from the *All of Us* Research Program will accrue over time and will primarily advance future disease prevention and treatment strategies. There is no guarantee that the participant will directly benefit. However, potential indirect benefits to participants in the *All of Us* Research Program include:

8.2.1 Access to Information

Initially, participants will have access to their physical measurements and PPI responses via the Participant Portal. As new information types are collected, we will seek to provide access via the Participant Portal in the spirit of the Program's values (see Section 2.1, What Is the *All of Us* Research Program?). Empowering participants with information and data may help to improve their own health.

8.2.2 Screening Physical Measurements

Participants who undergo physical measurements will receive their personal data, along with information about the normal ranges. They will be told when their measurements are outside the norm. Participants may benefit from increased awareness of their health status and identify issues that warrant discussion with a health care provider (e.g., elevated blood pressure that, if confirmed, may warrant lifestyle modification or antihypertensive medication).

8.2.3 Opportunity to Participate in Ancillary Studies

Eligible participants may be contacted about opportunities to participate in research studies relevant to their health or interests. They may also be invited to participate in clinical trials of targeted interventions and therapies of which they otherwise would not be aware.

8.3 **Risk/Benefit Analysis**

The goal of the *All of Us* Research Program is to create a public resource for biomedical investigation and a research infrastructure that can be leveraged to improve human health. As noted above (Section 8.1, Risks), we acknowledge potential risks that may be incurred by study participants as well as strategies in place to minimize these risks. Although benefit to individual participants is not a specific aim of the *All of Us* Research Program, participants may nonetheless derive indirect benefits (Section 8.2, Benefits). Taken together with the scientific value of the program, we believe that the overall benefits outweigh the risks of participation.

9. Ethical Considerations

The program will be conducted in accordance with the principles of the Declaration of Helsinki and the Common Rule.

9.1 **Payment for Participants**

Participants will be offered \$25 for their participation, following completion of the in-person physical measurements and biospecimen collection. Participants who need to complete these procedures in multiple visits will be paid upon the final visit. Provisions will be made for participants who decline payment. In addition to the \$25 payment, participants may be eligible for transportation or parking costs, based on the site-specific business practices of their enrollment location. If the participant withdraws his/her participation, s/he will not be expected to return the \$25.

Data collected in the *All of Us* Research Program may be used to discover or create new products, or tests, and some of these may have commercial value. Participants whose data have been used to create these products or tests will not be compensated by NIH, the program, scientists, or institutions that may benefit from these commercial products. The program data will not be sold/distributed for commercial benefit or for marketing purposes outside of the *All of Us* Research Program. The AURAC (*All of Us* Resource Access Committee) will serve as steward of the resource.

No serious injuries are anticipated as a result of participating in this study. However, if a participant is injured as a direct result of their involvement in the *All of Us* Research Program:

- The *All of Us* Research Program will pay for the cost of immediate medical care to treat the injury. The participant will be responsible for none of these costs. Cost of immediate medical care for injury will be evaluated according to institution-specific protocol. Institutions may bill the participant's insurance at their discretion.

- If the research injury requires medical care beyond the immediate treatment, cost of follow-up care may be billed to the participant and their insurance. If the participant does not have insurance or if the insurance will not pay, the participant will be responsible for these costs
- Participants will not be otherwise compensated for the injury.

9.2 Genetic Analysis Ethical Considerations

Participants who provide a biospecimen may be invited to participate in genetic analysis at a future date. A specific genetic consent module will be developed and submitted for IRB review to enable participants to opt into the genetic analysis.

9.3 Handling On-Site Adverse Events

The *All of Us* Research Program clinical partners will provide appropriate accreditations and policies and procedures—and will ensure appropriate training of all program staff—to assure appropriate processes for responding to situations when physically working with the *All of Us* Research Program participants in their clinics or at their facilities. These policies and procedures will be collected by the NIH Program Officers and filed as part of Institution-Specific IRB Applications to this Core Protocol. It will be important to ensure that the all clinical partner sites have procedures in place for incidents such as:

- Physical injury that occurred while on site or during the act of the physical measurements and/or blood draw
- Verbal and nonverbal indications that the individual may be a victim of physical and/or emotional abuse
- Indications of suicidal thoughts
- Misconduct on the part of the participant that negatively impacts the center/clinic or its patrons

9.4 Withdrawal Procedures

Participants may, at any time, withdraw their participation from the *All of Us* Research Program without giving a reason and without penalty. They may do this by selecting the withdrawal option on the web or mobile application or by notifying the Support Center, who will guide them to withdraw through the Participant Portal. In addition, investigators may discontinue a participant if necessary and for any reason, including ineligibility arising during the program or retrospectively if overlooked at enrollment.

The withdrawal status of a given participant should be recorded within the *All of Us* Research Program database within 2 business days. Confirmation of withdrawal will be provided to participants via email and/or letter. Participants will be informed upon enrollment that their name and basic contact information will never be destroyed, even after withdrawal, due to regulatory requirements (e.g., as part of archived consent forms); however, the information will be maintained with the utmost security. The participant's records will be flagged to show the participant withdrew and does not want to be contacted. Participants who withdraw will no longer be contacted about follow-up opportunities, and no additional information will be collected about them. The participant's

record will no longer be available through the Participant Portal. The participant's record will be maintained in HealthPro, but only the following data will be retained: participant ID, first name, last name, date of birth, date of consent, and date of withdrawal. All other data will be deleted from the HealthPro record. The purpose of maintaining this subset of data for withdrawn participants in HealthPro is to ensure that site-specific databases at the HPOs maintain accurate records on the status of withdrawn participants. HPOs can thus take care to not proactively approach or otherwise contact (via any modality, including phone, email, or text) withdrawn participants and can maintain records of all participants to whom \$25 was distributed.

Participants are informed during the consenting process that data/specimens previously collected and already used in research cannot be withdrawn nor destroyed. For instance, it is not possible to destroy all sample remnants and information already distributed or analyzed. In contrast, stored biospecimens that have not been analyzed or distributed to qualified researchers will be destroyed. Existing datasets, including data from withdrawn participants, will remain available to promote reproducibility of research, an NIH priority. However, no new data or samples will be collected.

Re-enrollment in the program is allowed. However, participants who re-enroll after withdrawal will need to create new participant entries and donate new biospecimens. They will not receive \$25 for their return participation following completion of the new in-person physical measurements and biospecimen collection.

Note: At program launch, we will have implemented the process and code for withdrawal only. In the future, we also plan to develop “no contact” options for participants. We will notify the IRB when we have completed the infrastructure to support such options.

9.5 Destruction of Specimens

Because blood samples could potentially contain biohazardous materials, the central program laboratory will not be able to return unused specimens back to participants or their families.

In an effort to respect participants' values and beliefs, the *All of Us* Research Program will enable a cultural ceremony performed by an accredited tribal healer or medicine man to administer blessing or last rites to samples prior to their destruction. Additional site-specific processes for culturally sensitive practices may be developed and approved through Institution-Specific IRB Applications. This option is available to any participant who requests it. This selection can be made at any time throughout the program. It is estimated that such cultural ceremonies will take place twice a year at the central laboratory. Samples tagged for destruction under this option will be stored until the ceremony takes place.

The central laboratory will dispose of biological specimens in accordance with [Occupational Safety and Health Administration](#) (OSHA) medical waste disposal guidelines.

10. Access to Individual-Level Information for Participants

10.1 Principles of Individual-Level Information Availability

The *All of Us* Research Program information access procedures, including access to data and results, will adhere to principles outlined by the White House’s [Precision Medicine Initiative: Privacy and Trust Principles](#) and [Data Security Policy Principles and Framework](#), including transparency, timeliness, and participant empowerment.

- Uncertainty of meaning or concern about impact on participants should not be a reason for the *All of Us* Research Program to withhold information from participants.
- Where possible, information must be presented in a culturally appropriate and language-specific manner.
- The default bias for information access must always be to make the information available to participants as soon as possible.
- The choice to access and review information will be at the discretion of the participant. When possible, participants must be able to set preferences for the type, method, and frequency of information they may receive, and will be allowed to change these preferences at any time.

As individual-level information becomes accessible, it needs to be readily and easily available to participants, in an array of data-specific and results-specific formats and interfaces that may include:

Data-specific formats and interfaces:

- Hard copy of the physical measurements. A template form will be used to give participants their physical measurements.
- Machine-readable/structured data available for direct download and through application program interfaces (APIs).

Results-specific formats and interfaces:

- Visual/interface-based tools and interactive dashboards. Participants can view results through their program account on the secure Participant Portal.
- Multiple information-sharing platforms and interfaces will be created to provide flexibility for access to individual level results (e.g., infographics, web-based dashboard, mobile apps, newsletter, email, mail, etc.). These platforms may also be used to return group- and program-level results.

We anticipate that participants’ access to their own information—including their experience throughout that process—is a critical component for maintaining their long-term engagement with the program.

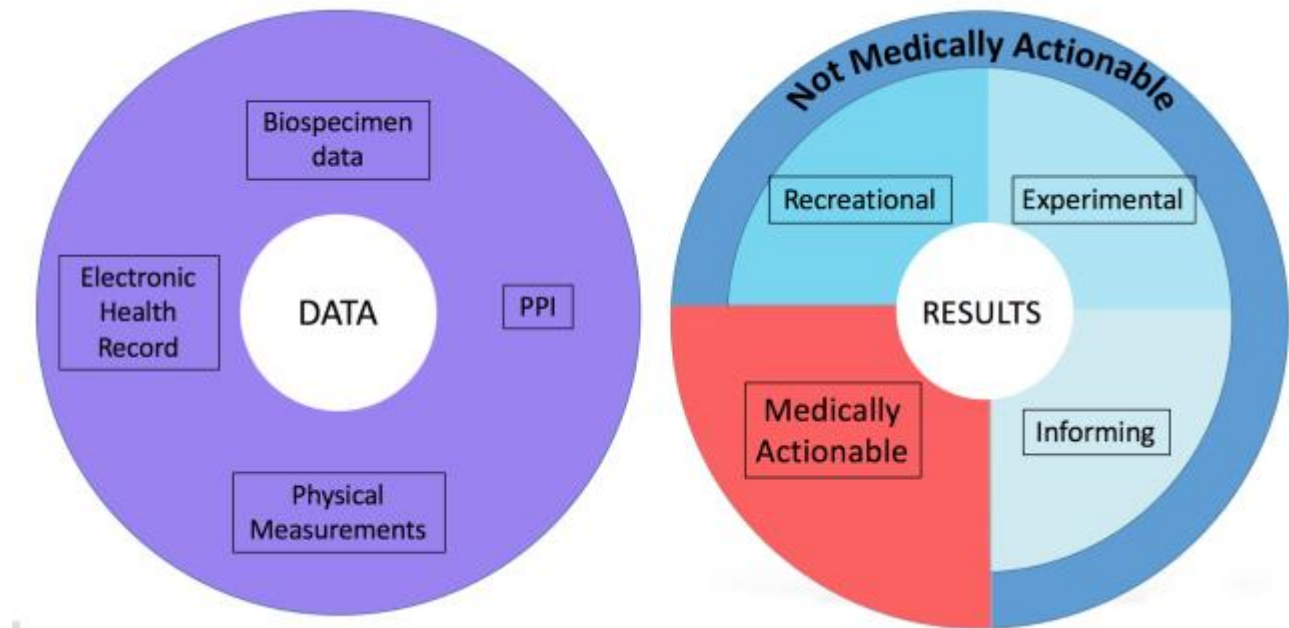
10.2 Individual-Level Program Information

The *All of Us* Research Program will gather and generate a tremendous amount of information about each participant as an individual. Individual-level program information falls into two categories: data and results.

Individual-level data includes all information that participants contribute (e.g., PPI, physical measurement data, EHR data), as well as data that is generated from biospecimens (e.g., genetic sequence data from a participant’s sample) (Section 10.2.1). Consistent with the core principles of the program, participants will have access to all of their individual-level data they contribute.

The second category of individual-level program information is results. Individual-level results are the interpretation of specific participant data. These results fall into two main categories: medically actionable and not medically actionable.

Figure 10–1: All of Us Research Program Individual-Level Information: Data and Results



10.2.1 All of Us Research Program Individual-Level Data

Consistent with the core values of the *All of Us* Research Program, participants will have access to all of their contributed program data and individual results. Participants may contribute:

- PPI responses
- Physical measurements
- Electronic health records and Part 2 records
- Biospecimens
- Other types of data in the future, such as sensor measurements

Data derived from these contributions, such as genetic sequencing data and wearable sensor data, are considered individual-level data. In addition to instances of aggregate-level readouts of the individual-level data, data will be available to participants in “raw” form, without interpretation. Participants are empowered to decide if and when to access their individual-level data. They will not have to receive such information but will have the option to do so if they choose to. The exception to this would be data derived from studies whose data is not necessarily resolvable at an individual level or is not considered a test

with high validity. An example might be a new genetic test that developed sequence data for a population but not an individual, or a lab test whose error rate on an individual was particularly high (likely due to it being a very new test without a reliable alternative). It is thought that such considerations would be rare, as in general, we will seek use of reproducible tests with high validity.

10.2.2 All of Us Research Program Individual-Level Results

Medically actionable results are results that could be used to inform the medical care that participants seek or receive to maintain their personal health. Participants may need to complete a supplemental consent process or some other informing interaction prior to unlocking their medically actionable results. An example is an emergent blood pressure measurement.

Not medically actionable results are results that could inform participants' decision making but not directly inform the medical care that participants seek or receive to maintain their personal health. Examples of not medically actionable results are:

- Measurements within an expected range (i.e., "normal" cholesterol)
- Recreational results, such as taste aversion
- Experimental results from novel assays

It is important to note that not all participants will choose to receive their individual-level results. Participants will be free to share their results with anyone they choose. The rationale for not contacting the participants' health care providers directly include:

1. Not all participants will have a health care provider, as may be the case specifically with DV participants.
2. This is not a clinical study; it is an observational study.
3. All participants should be treated with the same standardized protocol. We feel that the Participant should have the freedom to make the decision of when and how to communicate individual-level results information to their health care provider if they choose.

In order to facilitate understanding and sharing their results, we will develop easy-to-read templates.

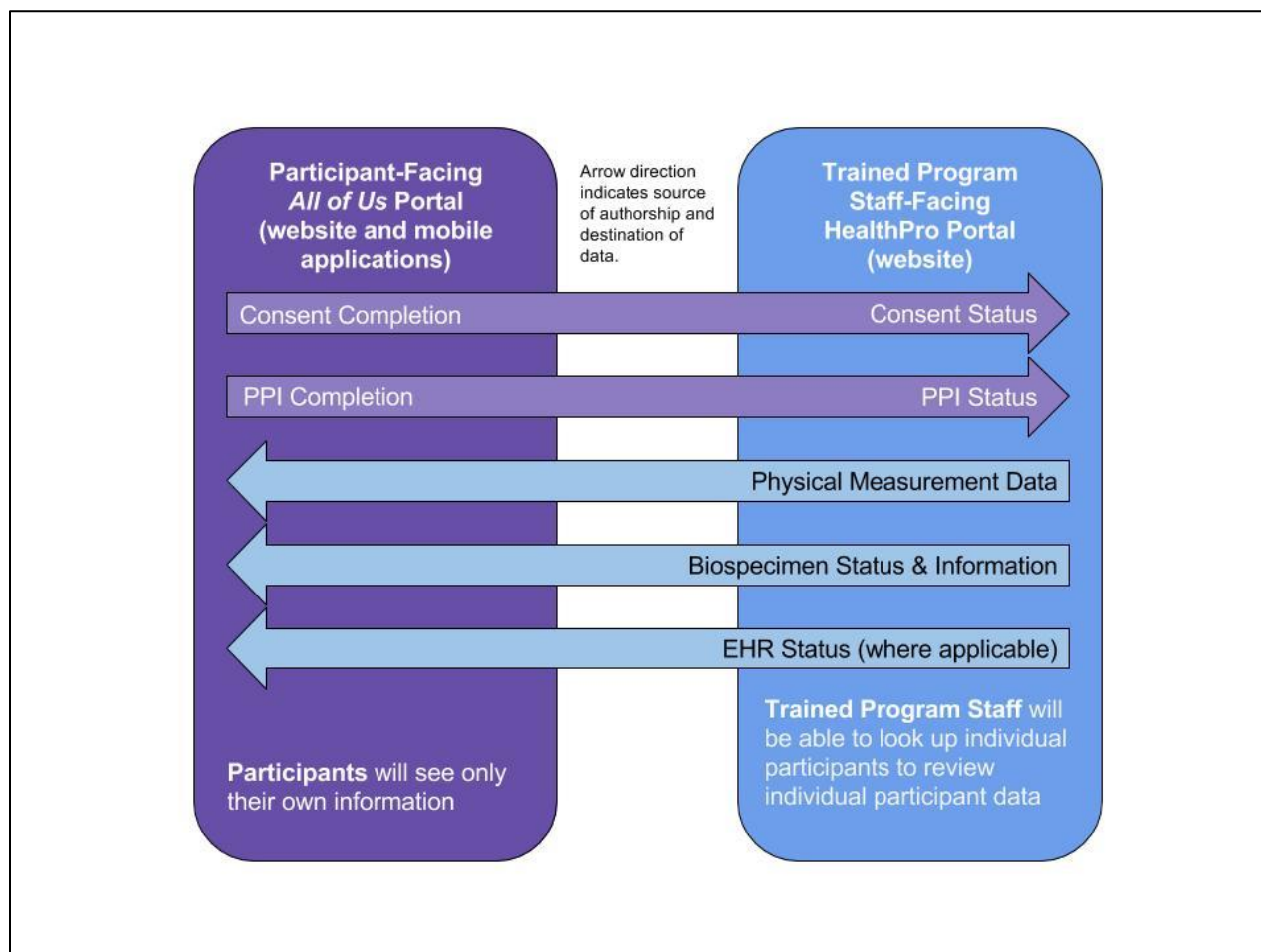
10.2.3 Return of Results: Framework

The *All of Us* Research Program is beginning to develop a framework and set of processes for returning results to participants. This framework will:

- Lay out the principles for returning *All of Us* Research Program data and results to participants
- Establish guidelines for applying the framework to existing and new data and result types
- Develop data and results type-specific access and return policies (which will grow over time), allowing for a participant's individual preferences in what types of data they would like to see or have actively returned to them.

10.3 Information Access Technologies

Figure 10–2: Data Flow for Participants and HPO Staff



10.3.1 All of Us Research Program Participant Portal

The core public-facing program enrollment and communication tool is the program's Participant Portal. In addition to providing program updates and messages to participants as described above, participants can access their individual-level information on their personal account using this portal. A future portal version will include a dashboard where participants can view their data (PPI and physical measurements) compared to the aggregated data generated through the *All of Us* Research Program.

Furthermore, the DRC will maintain the Research Portal to enable access to the program data, including a public portal where participants will be able to view aggregate data and a registered access portal where participants, as citizen scientists, will be able to access de-identified data.

10.4 Individual-Level Information Access Processes

10.4.1 Physical Measurements—Access to Information

In the spirit of the *All of Us* Research Program values (Section 2.1, What Is the *All of Us* Research Program?), all physiologic and anthropometric measurements logged through the physical measurement process will be stored in the “Participant Record” through the PTSC application (web and mobile) and will be accessible by the participant at any time. Once the participant completes their physical measurements, the data will be accessible through the Participant Portal and through hard copies provided by trained program staff at time of physical measurement, if preferred by the participant. A template form (hard copy) will be used to give participants their physical measurements in a consistent manner.

As described above (Section 7.3, Physical Measurements), the physical measurements will include physiologic (e.g., blood pressure and heart rate) as well as anthropometric (e.g., height, weight, waist and hip circumferences) measurements. Body mass index will be calculated automatically from measured height and weight.

Participants will also receive the aggregate-level measurement values from publicly available information until there is a critical mass to provide an equivalent comparison using program data.

Another goal of the *All of Us* Research Program is to couple the information with educational materials to promote understanding. These educational assets may include:

- Normative values and evidence-based guidelines for components of the physical measurements specifically focused on the individual’s demographics, such as sex, age, and race.
- Links to websites (e.g., WebMD or PatientsLikeMe) that provide information pertaining to each measurement.
- The *All of Us* Research Program will produce educational videos (to be developed) that provide background information on the various components of the physical measurements collected through the program.

The *All of Us* Research Program is an observational study, and therefore none of the information provided constitutes clinical recommendations. Every effort will be made during communications to potential participants to clearly state that the *All of Us* Research Program is an observational study and is not designed to diagnose or treat any medical condition or serve as a substitute for regular medical care. Participant information access modalities will provide a disclaimer that the participant may wish to consult a health care provider to follow up on physical measurement information, and any questions the participant has about impact of program-related information on their personal health or clinical management should be directed to their health care provider. If a participant does not have a regular provider, the trained *All of Us* Research Program staff will provide referrals at participant request to appropriate care options in their region.

10.4.2 Notice of Future Amendment to Core Protocol

As the public-facing and individual participant information dashboards are developed, they will be presented as an amendment to the core protocol, to provide the IRB with the opportunity to provide guidance.

10.5 Physical Measurements—Return of Medically Actionable Results

Although the physical measurement component of the *All of Us* Research Program does not constitute clinical care, we anticipate that a small but important percentage of individuals will have medically actionable results that, if left unaddressed, might have adverse consequences for the participants' health.

Clinically actionable findings from the physical measurements are limited to blood pressure and heart rate, as defined below (Table 10–1: Medically Actionable Findings at the Time of Baseline Physical Measurements). Trained program staff will record physical measurements via HealthPro. If a measurement falls outside the range considered “normal” per the *All of Us* Research Program Protocol, a message will pop up on the HealthPro screen. After confirming the measurements, the trained program staff will ask the participant whether these measurements are typical. The following script was developed to guide discussion about measurement findings with the participant and draw attention to certain measurements:

Trained program staff:

- I’ve taken your (blood pressure or pulse) three times, and at least two out of those measurements returned a value that is typically considered to be outside of what is commonly referred to as a “normal range.”
- This does not mean that it is necessarily a concern, as it may just be how your body naturally is.
- Have you experienced a reading similar to this in the past? If so, is that reading considered standard for you?
 - Yes? Would you say that your health care provider would agree that this is a typical reading for you?
 - Yes? Okay, good. I’ll just note it on the handout and we can move on
 - No or I don’t know? <assume that this is an actionable finding and respond according to the responses noted in Figure 10–3: Physical Measurement Card and the site’s organizational policies and procedures>
 - No? You have not received a reading like this before (or you don’t know)?
 - <assume that this is an actionable finding and respond according to the responses noted in Figure 10–1 and the site’s organizational policies and procedures>

Participants requiring immediate and expedited referrals will be managed per institution-specific policies and procedures, as declared in the Institutional-Specific IRB Application. Similarly, if, in the opinion of the trained program staff performing the physical measurements, the participant appears to be clinically unstable for any reason, site-

specific policies and procedures will be followed. These site-specific policies and procedures will be collected and reviewed by the NIH Program Officer and can be provided to the IRB upon request.

Table 10–1: Medically Actionable Findings at the Time of Baseline Physical Measurements

	Emergent	Urgent
Systolic Blood Pressure*	<ul style="list-style-type: none"> • >200 mmHg • <100 mmHg and any symptoms of hemodynamic instability*** 	<ul style="list-style-type: none"> • 180–200 mmHg
Diastolic Blood Pressure*	<ul style="list-style-type: none"> • >120 mmHg • <60 mmHg and any symptoms of hemodynamic instability*** 	<ul style="list-style-type: none"> • 110–120 mmHg
Heart Rate**	<ul style="list-style-type: none"> • Heart rate <60 or >100 and any symptoms of hemodynamic instability*** • Heart rate <60 or >100 and hypotension (systolic blood pressure of <90 mmHg) without symptoms of hemodynamic instability*** 	<ul style="list-style-type: none"> • Asymptomatic heart rate <50 beats per minute or >120 beats per minute • Heart rate >100 beats per minute and irregular • Pulse unable to be determined via digital cuff (following verification by manual pulse determination when possible) unless confirmed by participant that an irregular heart rhythm is already a known condition
Minimum Site Response	Participant is immediately advised of the need of emergent care, and if agreed to by participant, trained program staff will refer them to emergency care (e.g., site-specific emergency room or 911); refusal will be documented according to site-specific policies and procedures.	Participant is immediately advised to seek medical attention and to notify their provider, or trained program staff may offer to help locate an urgent care facility and coordinate transportation to the facility as needed.

* Based on Seventh Joint National Committee (JNC 7) recommended blood pressure goals. [Hypertension 2003;42:1206-1252.]

** Based on the American Heart Association recommended target heart rates.

***Hemodynamic instability is defined by, and will be prompted within HealthPro at the time of data entry meeting numeric criteria, to include (1) changes in mental status (reduced alertness and awareness, confusion, possible loss of consciousness); (2) chest pain; (3) shortness of breath and/or rapid breathing; and/or (4) cold, clammy skin.

Emergent and urgent actionable findings will not be sent to a provider. Instead, a “Physical Measurement” document/card will be provided to the participant with their physical measurements, along with any urgent or emergent findings specifically called out. The participant can use this card to follow up with a provider of choice. Trained program staff

will use the script above to call the participant's attention to any emergent or urgent actionable findings listed on the card.

Figure 10–3: Physical Measurement Card

All of Us

Thank you for taking part in the *All of Us* Research Program.
By sharing your information, you're helping shape the future of health care.
This form has your physical measurements from your visit today.

Date of Visit: _____

Height: _____ **Weight:** _____ **Body Mass Index (BMI):** _____

Hip Circumference: _____

Waist Circumference: _____




Blood Pressure (Systolic/Diastolic): _____ / _____

Heart Rate (Beats per Minute): _____

You will see blood pressure and heart rate information on the right. This is to give you a broad sense of what is thought to be “normal” for an average person. Your “normal” may be different from this for many reasons. These reasons may include your age, level of fitness, and general health. Concerns or questions about your measurements? Please speak to your health care provider or contact the *All of Us* Support Center at 1-844-842-2855 or help@joinallofus.org.

The National Institutes of Health offers many resources to help people learn more about heart health. It also has tools to help people maintain a healthy weight.

Visit: <https://www.nhlbi.nih.gov/health>.



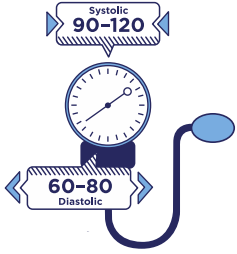
☐ Your preliminary findings suggest a potential concern with your blood pressure _____ / _____ or heart rate _____.
We recommend an evaluation by a health care provider as soon as possible.

Adult Body Mass Index (BMI) Groupings:


BMI is less than 18.5	BMI is 18.5 to 24.9	BMI is 25 to 29.9	BMI is 30 or more
underweight	normal	overweight	obese

(These apply to both men and women.)

Normal Blood Pressure Range:



Normal Heart Rate Range:



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joinallofus.org

HPOs/DV sites will access the template for the “Physical Measurement” card via the Wondros Asset Portal. All HPOs/DVs will be responsible for printing the document and making it available to their sites.

10.6 Participant-Provided Information and EHR

Participants will provide various types of information to the program through questionnaires and other modules, which may include demographics, disease state, health information/lifestyle, data type, and/or location. A future version of the Participant Portal will include a dashboard where participants will be presented with a comparison of how their information lines up with aggregate-level information from the *All of Us* Research Program.

EHRs from DV participants will be integrated into the platform at a future date; see Section 7.6, Electronic Health Records (EHRs).

10.7 Access to Biospecimen-Derived Information (Non-Genetic)

10.7.1 Biospecimen Collection—Access to Information

In the spirit of the *All of Us* Research Program values (Section 2.1, What Is the *All of Us* Research Program?), all biospecimen participant information provided to or generated by The program will be accessible to the participant in an appropriate, IRB-approved manner.

Participants will be able to access their biospecimen-derived information upon request. There will be information pertaining to the status of the biospecimen and information pertaining to biospecimen-derived data if applicable, as described below.

10.7.2 Information on Biospecimen Status

Participants who opt to keep informed about their biospecimen status via the secure Participant Portal may receive the following:

- A message thanking them for their donation
- Notification that their biospecimen has been received by the Biobank (e.g., “Congratulations, your specimen is in the Biobank”)
- Educational information pertaining to the “journey” that their biospecimen donation will take (e.g., collection clinic/center to Biobank to being de-identified and sent to a research database)

10.7.3 Biospecimen-Derived Data—Notice of Future Addenda to Core Protocol

Due to the wide number of assays that may be performed on biospecimens over the course of the program, it is impossible to adequately account for all potential types of information that may be generated, including “normal” and “abnormal” range findings and potentially clinically actionable information. Therefore, the program will implement a

process whereby, as a specific assay is being planned, an information access plan will be developed in tandem and submitted to the IRB for review prior to initiation of that assay.

10.8 Access to Genetic Information

It should be noted that at launch of the *All of Us* Research Program, neither genetic assays nor their consent are being performed. Plans for genomic assays will be developed subsequently, and an accompanying policy for access to genetic information will be provided to the IRB.

11. Creation of the *All of Us* Research Program Resource

A primary end product of the *All of Us* Research Program is a curated dataset that will be made available to support scientific investigation. Multiple streams of data will flow into the DRC, including PPI, data from physical measurements, biospecimen measurements, EHR data, and data obtained through linkage with distinct datasets (e.g., the Social Security Death Index) as outlined in Section 7.7 (Data Linkage).

Figure 11–1: Curated Dataset



The DRC will integrate data streams into a Raw Data Repository in real time. Incoming data will be associated with participant IDs. This data will be transformed into a Curated Data Repository that includes minimally identifiable information. This transformation approach will include validation and implementation of phenotyping algorithms that extract variables of interest (e.g., diagnosis of coronary artery disease).

This curated dataset will exist in a secure cloud-based analytic platform to support analyses of interest. This environment will be equipped with an elastic pool of compute resources and a framework for using third-party applications. Importantly, this differs from the model of traditional research repositories, where data resides on a server and is then downloaded to a local infrastructure—i.e., the *All of Us* Research Program will encourage future researchers to “bring the analysis to the data” rather than bringing “the data to the analysis.”

Advantages of this approach include:

1. Security—Significant centralized resources can be brought to bear to secure copies of the data, and access can be more easily monitored and tracked by removing data “handoffs.”
2. Cost—This avoids the need to store multiple copies of the massive dataset.
3. Accessibility—Few groups have the infrastructure needed to support data on this scale, limiting its utilization.
4. Elasticity—We can provide a pool of compute resources for needs that vary over time.

The curated dataset will underlie information provided to individuals via the Participant Portal. Approved researchers will query this dataset. The same curated dataset will be used to inform the *All of Us* Research Program leadership about program progress.

12. Post-Enrollment Engagement Strategy

The mission of the *All of Us* Research Program is “to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care.” Meaningful post-enrollment engagement with and retention of participants is critical to fulfilling this promise.

For the purposes of the program, *engagement* is used as an overarching inclusive term to describe the broad range of interactions between the program, people, and awardees and other organizations. Engagement includes information sharing, consultation, involvement and collaboration in decision-making, and empowered action in informal groups or through formal partnerships. Consistent with the program’s values (Section 2.1., What Is the *All of Us* Research Program?), the engagement strategy is focused on empowering individuals and communities through greater access to information and data. This participant-focused engagement strategy may also improve the quality and quantity of data contributed to the *All of Us* Research Program.

Specifically, post-enrollment engagement differs from outreach for recruitment in that engagement provides the opportunity to interact with partners, where the outcome may be a bidirectional increase of general knowledge and increased partner input.

Retention describes efforts to encourage and support ongoing contribution to the program by participants. “Contribution” includes a broad set of actions to improve the amount and quality of data in the repository, from the donation of additional participant-provided information and reflection on and refinement of participant records by participants themselves, to the sharing of experiential feedback for the improvement of the program. Effective retention will improve the quality of quantity of data provided by participants and as such will improve the value of the *All of Us* Research Resource for all scientific uses. Retention will also benefit engagement efforts in that the repository may then be a more meaningful resource for participants as individuals and at the community and national levels.

Given the unprecedented scope and scale of the *All of Us* Research Program, we recognize that there is currently no proven, effective long-term engagement or retention strategy for this type of very large longitudinal cohort program. Whenever possible, all strategic initiatives around engagement and retention will be designed as learning programs to enable effectiveness testing and will be informed by existing research efforts in community-engaged research.

12.1 Conceptual Framework

Framework discussions about engagement and retention often begin with examinations of motivation: Is someone extrinsically motivated to participate in *All of Us*, or intrinsically motivated? Extrinsic motivations often take the form of direct payment but can also be longer-term “games” in which people accrue tokens such as points, badges, or “swag” in return for continued participation. Intrinsic motivations are often described via conceptual frames, such as relatedness, autonomy, proficiency, or purpose.

Intrinsic motivations are generally found to last longer, increase engagement, and increase adherence compared to extrinsic motivations (Boundless, 2016). There is also sometimes an inverse relationship between the two, in which receiving an explicit reward can short-circuit implicit motivations.

Within the Community Engagement Studios performed at Vanderbilt to inform development of the project, participants did not hesitate to ask for extrinsic “incentives” to encourage their participation. The balance between intrinsic and extrinsic motivating forces in human subjects research leans away from extrinsic motivators and skews heavily to intrinsic motivation as a way of avoiding the hazards of undue influence and involuntary participation. By contrast, modern digital apps are designed for “stickiness”—the ability of an app to repeatedly bring its audience back into the app.

In our complete engagement and retention plan, we will list the various approaches, with notations on where there are complex interactions between them, as well as mitigation strategies where appropriate. Working from this conceptual framework allows us to specifically examine outreach efforts to ensure the program is motivating but not coercive—honoring the principle of informed consent in human research.

12.2 Approach to Engagement

The *All of Us* Research Program explicitly values participants as partners in research (Section 2.1, What Is the *All of Us* Research Program?). We strive toward that partnership by creating an engagement strategy with participant partnership built intentionally into its structure. Engagement in the program will be a systematic, considered process, with the express purpose of working with groups of people—whether they are connected by geographic location, special interest, health condition, affiliation, or identification with issues affecting their well-being. The overarching goal of our engagement strategy is to create a program reflecting the needs, preferences, and priorities inclusive of the range of age, social, racial, ethnic, cultural, geographical, and health statuses of individuals across the program. Participants and their advocates will be involved in all aspects of the program, including governance, oversight, design, conduct, dissemination, and evaluation. We aspire toward maximum inclusiveness to ensure that all communities are respected and represented.

The word *community* is broadly intended to define groups of people such as participants, stakeholders, special interest groups, and citizen groups. Communities for the program may develop due to shared circumstances or interests of any kind—for example, geographic location, racial/ethnic identity, cultural group, shared beliefs, or experience with or interest in particular health conditions.

The engagement strategy will be designed to encourage multidirectional communication and participation in the program by individuals—those participating, their advocates, and interested community members—and organizations. As such, engagement strategies will be threaded through awareness, recruitment, enrollment, and retention activities. Key elements of the strategy include but are not limited to the following:

- Regular reminders to sites' Principal Investigators and point of contact people of the program's core values
- Verification of budget allocation to support impactful and inclusive engagement and retention strategies at all stages of the program
- Having 1 or 2 key personnel who are knowledgeable, culturally competent, sensitive, and personally accountable for the successful implementation of the engagement efforts
- Working collaboratively with engagement experts and sharing information and best practices
- Promoting a Community Emotional Quotient Approach (CEQ) that resonates with the population served—i.e., designing an engagement approach that incorporates key elements attuned to and responsive to the needs of the community
- Designating key engagement voices as representatives on participant-facing committees, task forces, and work groups

We present some example engagement activities that will be undertaken at launch but that do not represent the complete or final engagement plan, outlining some initial tools and methods. We will submit a more developed engagement plan, including assessment metrics, to the IRB.

12.2.1 Examples of Interpersonal Engagement Activities

At the interpersonal level, we will leverage existing community health infrastructure to support meaningful engagement. For example, the New York Regional Medical Center (RMC) will use its Each One Teach One programming, where health topics are identified by a steering committee of community members; health information is then delivered back to the community via person-to-person conversation and through the web by medical experts. The Pittsburgh RMC created the multimedia Pitt+Me engagement platform to provide information about research generally and raise awareness of specific studies that may be of interest to community members. Overall, these regional initiatives promote personal positive experiences with study participation, fostering empowerment at the interpersonal level.

12.2.2 Examples of Community-Level Engagement Activities

Awardees will leverage local health centers and community gathering places (e.g., local pharmacies, blood banks, churches), including the specifically designed Mobile Engagement Asset (MEA) described previously, to engage participants at the community level. For example, New York's "Come meet *All of Us*" will be its first engagement event and will include both an introduction to the *All of Us* Research Program and an opportunity for community members, scientists, providers, practitioners, and partners to meet and interact with the team who are bringing the program forward in the community. Pitt's partnership with the Urban League of Greater Pittsburgh and more than 150 community organizations through its CTSA program will be leveraged to promote the *All of Us* Research Program at the community level throughout western Pennsylvania. The VA intends to provide connection to the *All of Us* Research Program through informational/conversational kiosks at various community gatherings and events, in addition to other material relevant to the health of veterans. The program will collect community and participant input through surveys and shared stories. More engagement opportunities will be developed with partners as part of the funding proposal: <https://www.nih.gov/research-training/allofus-research-program/funding/all-us-research-program-engagement-partners-ot2>.

12.2.3 Examples of National-Level Engagement Activities

At the national level, we have many dissemination channels for official program materials. Most RMCs have tailored websites that have the capacity for two-way communication. Wondros' *All of Us* Research Program campaign, which will include digital messaging, will be used to engage participants. Targeted special campaigns would also help keep communities of shared interests together. The VA plans to engage well-known, well-respected leaders in the veteran community to discuss importance of the *All of Us* Research Program to veterans across the country; this approach could be expanded to other national-level communities who are joined by special interest or identity.

12.3 Retention

Long-term retention of participants is by far the greatest challenge to achieving the most ambitious scientific goals of the *All of Us* Research Program. There are several notable examples of successful longitudinal cohort studies with high retention rates over decades,

such as the Framingham Heart Study and the Nurses' Health Study, both with around 90% retention of study participants 2 to 3 decades after enrollment. Both of those programs require active involvement by participants only every 2 years, with the Framingham cohort undergoing an in-person exam and the Nurses' Study one by mail. The *All of Us* Research Program poses unique challenges relative to these successful examples, well beyond its much greater size. Unlike Framingham's, the participants in the *All of Us* Research Program will be far more geographically diverse, scattered across the United States and U.S. territories, and without the benefit of required recurring in-person visits. The Nurses' Health Study differs in that it is made up of a relatively homogeneous population of individuals with a professional tie to health care, unlike the diversity of backgrounds of participants sought for the *All of Us* Research Program. Due to the scale and geographic spread of the program, retention strategies will be primarily digital but will also include "analog" outreach to ensure retention of the broadest cohort of participants.

12.3.1 Digital Approaches to Retention

A digital retention strategy is made possible by today's ubiquitous connectivity via mobile technologies, including smartphones—which are currently owned by two thirds of all adults in the United States—and personal computers. Due to the scale and geographic range of the program, we anticipate that most long-term interactions with the program will be digital; thus, the web and mobile application have been designed to be user-friendly and engaging, with a responsive and intuitive user interface.

12.3.2 Non-Digital Approaches to Retention

Digital connectivity is not sufficient to establish a high level of retention. For example, the largest experience with mobile device medical research, Apple's ResearchKit, has shown active retention rates of close to only 10% in the months following initial enrollment. Further, non-digital methods will facilitate the retention of those who may not be comfortable with technology. The non-digital methods will include the Support (Call) Center, site-specific touchpoints/services, and other site-specific outreach. The success of long-term retention activities may vary based on the sociodemographics of the region where participants are enrolled. The suite of activities should include methods focusing on multiple levels (individual, interpersonal, community, national). Materials created to engage participants at these levels should be made available to all enrollment sites as best practices.

Non-digital retention strategies successfully employed by other long-term cohort studies include:

- Provision of a small card that has the name of the project with a toll-free contact number that participants can call to update locator information or see information on the project.
- Reminder calls to participants to keep them engaged in the project
- Birthday cards to participants from the program. Cards would provide the toll-free project number and encourage participants to stay in touch.
- Outreach telephone calls to a participant-designated friend/family member (if consented to contact)
- Home visits by trained program staff

- Exit packets
 - Enrollment certificates (recognition)
 - Referral cards for friends and family

12.3.3 Retention Metrics

To measure when, where, and how well retention efforts working inside *All of Us* Research Program, we plan to develop metrics for assessing retention over time. Some metrics will be similar across all sites—for example, counting the number of survey modules completed. Other metrics will be specific to subpopulations within the program. For example, for those who download and use the program mobile application, we will be able to measure electronic interactions like login frequency, time spent, etc. Additional retention metrics may include:

- Responsiveness to requests to share additional participant-provided information, indicated by either actively accepting or declining an invitation (electronic or in person)—for example:
 - Invitation to provide routine updates regarding health status
 - Invitation to provide updated contact information as needed
- Responsiveness to communications for involvement in the *All of Us* Research Program by opening/viewing such communications

Additionally, it is recognized that there is no one-size-fits-all retention strategy, so part of the learning process will be how to best individualize retention strategies to best meet the needs of the individual.

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